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☐ 1. Document ID: US 6255290 B1

L2: Entry 1 of 3 File: USPT Jul 3, 2001

US-PAT-NO: 6255290
DOCUMENT-IDENTIFIER: US 6255290 B1

TITLE: Antimutagenic compositions for treatment and prevention of photodamage to skin

DATE-ISSUED: July 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
von Borstel; Reid W.	Potomac	MD		
Romantsev; Fedor	Gaithersburg	MD		

US-CL-CURRENT: 514/45; 424/450, 514/43, 514/44, 514/46, 514/47, 514/48, 514/49, 514/50, 514/51, 514/52, 514/844, 514/847 , 514/848

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 5770582 A

L2: Entry 2 of 3 File: USPT Jun 23, 1998

US-PAT-NO: 5770582
DOCUMENT-IDENTIFIER: US 5770582 A

TITLE: Pharmaceutical compositions containing deoxyribonucleosides for wound healing

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
von Borstel; Reid Warren	Kensington	MD		
Bamat; Michael Kevin	Chevy Chase	MD		

US-CL-CURRENT: 514/45; 514/46, 514/47, 514/48, 514/49, 514/50, 514/51, 514/944, 514/969

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 5246708 A

L2: Entry 3 of 3 File: USPT Sep 21, 1993

US-PAT-NO: 5246708
DOCUMENT-IDENTIFIER: US 5246708 A

TITLE: Methods for promoting wound healing with deoxyribonucleosides

DATE-ISSUED: September 21, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
von Borstel; Reid W.	Kensington	MD		
Bamat; Michael K.	Chevy Chase	MD		

US-CL-CURRENT: 424/450; 514/43, 514/45, 514/46, 514/47, 514/48, 514/49, 514/50, 514/51, 514/52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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L2: Entry 3 of 3 File: USPT Sep 21, 1993

DOCUMENT-IDENTIFIER: US 5246708 A
TITLE: Methods for promoting wound healing with deoxyribonucleosides

Brief Summary Paragraph Right (1):
This invention relates generally to the use of novel combinations of 2'-deoxyribonucleosides and 2'-deoxyribonucleotides and to the use of these compounds in pharmaceutical carriers to promote wound healing. More specifically, this invention relates to novel combinations of two or more of 2'-deoxyadenosine, 2'-deoxyguanosine, 2'-deoxycytidine and 2'-deoxythymidine and/or their corresponding nucleotides and their application, locally or topically in a mixture with carrier compounds to increase the supply of the active components to animal tissue and thereby to support cellular metabolic functions. Even more specifically, this invention relates to the use of mixtures of these compounds in carriers to promote and accelerate the healing of wounds, surgical incisions, lesions or ulcers of the gastrointestinal tract, burns induced by heat, ultraviolet light, or chemical agents, and superficial tissue damage caused by infections.

Brief Summary Paragraph Right (25):
The mixture of 2'-deoxyribonucleosides, preferably in pharmaceutical carriers, accelerate the rate of wound healing by delivering 2'-deoxyribonucleosides to areas of damaged tissue. The preparations of the invention may be administered in combination with any of a variety of conventional pharmaceutical carriers, ointments, gels, pastes, suppositories, sprays or irrigation solutions, or may be incorporated into carriers including liposomes, polymers or biodegradable polymers for gradual release, or from impregnated bandages, sutures, and similar materials.

Detailed Description Paragraph Right (13):
A preferred strategy is to administer these compounds locally or topically in gels, ointments, solutions, impregnated bandages, liposomes, biodegradable microcapsules or artificial skin containing the natural nucleosides. Unlike DNA, the deoxyribonucleosides contain no genetic information and are not antigenic. They are also chemically stable and can be purified easily and incorporated into a range of compositions. DNA, in contrast, is labile and easily broken into oligonucleotide fragments with random molecular weights and accordingly is unsuitable for incorporation in pharmaceutical preparations that require standards for uniformity and stability.

Detailed Description Paragraph Right (14):
Compositions or dosage forms for topical application may include solutions, lotions, ointments, creams, gels, suppositories, sprays, aerosols, suspensions, dusting powder, impregnated bandages and dressings, liposomes, biodegradable polymers, and artificial skin. Typical pharmaceutical carriers which make up the foregoing compositions include alginates, carboxymethylcellulose, methylcellulose, agarose, pectins, gelatins, collagen, vegetable oils, mineral oils, stearic acid, stearyl alcohol, petrolatum, polyethylene glycol, polysorbate, polylactate, polyglycolate, polyanhydrides, phospholipids, polyvinylpyrrolidone, and the like.

Detailed Description Paragraph Right (47):
1. PREPARATION OF LIPOSOMES CONTAINING DEOXYRIBONUCLEOSIDES

Detailed Description Paragraph Right (48):

Liposomes or other biodegradable vesicles containing deoxyribonucleosides may be utilized with advantage, in order to provide prolonged delivery of deoxyribonucleosides to wound tissues.

Detailed Description Paragraph Right (49):
The following protocol for liposome preparation was adapted from Szoka and Papahadjopoulos (PNAS 75:4194-4198 (1978)). Other methods for preparation of liposomes (and various other lipid components) may also be used to prepare vesicles containing deoxyribonucleosides.

Detailed Description Paragraph Right (50):
Cholesterol (50 micromoles), phosphatidylcholine (40 micromoles), and phosphatidylglycerol (10 micromoles) were dissolved in chloroform (5 ml) and diethyl ether (5 ml) in a 50 ml round-bottom flask. The flask was capped and purged with nitrogen. 1.5 ml of an aqueous solution containing deoxyribonucleosides, (e.g. 10 mg/ml of deoxyadenosine, deoxycytidine, deoxyguanosine, and thymidine in 15 mM NaCl) was added to the organic phase. The mixture was sonicated for 5 minutes at 0-5 degrees C. in a bath sonicator until the 2-phase system becomes a homogenous dispersion. A probe sonicator may also be used. The organic solvents were removed with rotary evaporator under reduced pressure (e.g. a water aspirator) at 35-40 degrees C., rotating at about 200 rpm. The mixture initially frothed, then became a viscous gel, and finally, it became an aqueous suspension. At this point, 2 ml of saline solution were added, and the suspension was evaporated for an additional 15 minutes to remove remaining traces of ether or chloroform. The preparation was then centifuged, to separate the liposomes from non-encapsulated material. 35 to 40% of the original deoxyribonucleoside solution was encapsulated within the liposomes. Following purification, the liposomes were concentrated by centrifugation, and suspended in 3 ml physiological saline for topical application to wounds.

Detailed Description Paragraph Right (51):
The deoxyribonucleoside-containing liposomes can also be suspended in ointments, creams, or other delivery vehicles for topical application to wounds, damaged skin, or ulcers.

Detailed Description Paragraph Right (52):
2. EFFECT OF LIPOSOMES CONTAINING DEOXYRIBONUCLEOSIDES ON WOUND HEALING

Detailed Description Paragraph Right (53):
Liposomes can be effective vehicles for the delivery of a variety of pharmaceutical compounds. The purpose of this experiment was to evaluate liposomes as potential delivery vehicles for the topical application of the deoxyribonucleosides to dermal wounds.

Detailed Description Paragraph Right (54):
Fourteen male F344 rats weighing approximately 200 grams each (8 weeks of age) were each given a standard, full-thickness 8 mm circular midline excision wound in the dorsal cervical region. A combination of deoxyadenosine, deoxycytidine, deoxyguanosine, and deoxythymidine (0.010/ml each) were incorporated into liposomes as described. Blank liposomes (made with saline solution only) or liposomes containing the deoxyribonucleosides were applied to the wounds on the day of surgery and once every 48 hours thereafter. Wounds were covered with a liquid plastic dressing as described by Marshak [Proc. Soc. Exp. Biol. Med. 58:63-65 (1945)]. Seven days after wounding, the wounds were examined macroscopically for the degree of granulation tissue formation and extent of re-epithelialization.

Detailed Description Paragraph Right (55):
The amount of granulation tissue present and the extent of new epithelium that had begun to cover the wounds treated with the nucleoside-containing liposomes was significantly greater than in the wounds treated with the blank liposomes only. These results show that liposomes containing deoxyribonucleosides are useful embodiments of the Invention.

CLAIMS:

25. A method for promoting wound healing comprising administering to an animal

possessing a wound a wound healing effective amount of a composition of matter comprising,

(a) from 10 to 90 percent by mol 2'-deoxycytidine, and

(b) from 90 to 10 percent by mol 2'-deoxyguanosine,

or the pharmaceutically acceptable salts thereof, in the form of a liposome.

29. A method for promoting wound healing comprising administering to an animal possessing a wound a wound healing effective amount of a composition of matter comprising,

(a) from 10 to 90 percent by mol of a 3'-or 5'-phosphate, or a 3', 5'-diphosphate ester of 2'-deoxycytidine, and

(b) from 90 to 10 percent by mol of a 3'-or 5'-phosphate, or a 3', 5'-diphosphate ester of 2'-deoxyguanosine,

or the pharmaceutically acceptable salts thereof, in the form of a liposome.

L3: Entry 6 of 44 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977083 A
TITLE: Method for using polynucleotides, oligonucleotides and derivatives thereof to treat various disease states

Abstract Paragraph Left (1):
Oligodeoxyribonucleotides, polydeoxyribonucleotides and derivatives thereof, such as defibrotide, are agents of genetic modulation at the levels of transcription, translation, secondary messengers and cellular signal transduction systems. Various disease states can be treated by modifying the dose of such agents in response to observed fluctuations (e.g., increase, decrease, appearance, disappearance) in normal, disease and repair markers.

Brief Summary Paragraph Right (1):
The invention relates to a method of using sequence non-specific polydeoxyribonucleotides, oligodeoxyribonucleotides and/or derivatives thereof, such as defibrotide, to treat various human disease states.

Brief Summary Paragraph Right (2):
Defibrotide is a polyanion salt of a deoxyribonucleic acid obtained from mammalian tissue. Defibrotide is a single-stranded polydeoxyribonucleotide with molecular weight of approximately 20 kDa (low molecular weight form) which may be obtained from bovine lung DNA by controlled hydrolysis. Patents related to its manufacture include U.S. Pat. No. 3,770,720 directed to a process for extracting DNA from mammalian tissue, and U.S. Pat. No. 3,899,481 directed to a process for the controlled partial degradation of DNA extracted from animal organs.

Brief Summary Paragraph Right (3):
Defibrotide is noted primarily for its profibrinolytic effects (Pescador et al., 1985, Thromb. Res., 30:1-11). Defibrotide increases the release of tissue-type plasminogen activator (t-PA) and decreases plasminogen activator inhibitor (PAI1) activity. The increase in t-PA is in conjunction with the decrease in PAI1, the latter being the more prominent action. The profibrinolytic activity of defibrotide is likely due to a decrease in PAI1 levels rather than to an increase in t-PA level (Pogliani et aL, 1987, Farmaci E Therapia IV, (2):1-5; Ulutin et al., International Scientific Symposium on Fibrinogen, Thrombosis, Coagulation and Fibrinolysis, Aug. 30-Sep. 1, 1989, Taipei, Taiwan, ROC).

Brief Summary Paragraph Right (4):
U.S. Pat. No. 3,829,567 is directed to the use of an alkali metal salt of a polynucleotide or an oligonucleotide of ribonucleic acid (RNA) and/or deoxyribonucleic acid (DNA) as a fibrinolytic agent. U.S. Pat. No. 4,649,134 is directed to a method of treating acute renal insufficiencies accompanied by thrombotic microangiopathy with defibrotide. Such pathologies include hemolytic uremic syndrome (HUS), collagenopathies (e.g., panarteritis and lupus), Wegner, Schoenlein-Henoch, disseminated intravascular coagulation (DIC), fast evolving glomerulonephritis, and thrombotic thrombocytopenia purpura (TPP). U.S. Pat. No. 4,693,995 is directed to a method of treating acute states of myocardial ischemia and infarction with defibrotide.

Brief Summary Paragraph Right (5):
While the primary target cell of defibrotide action has been shown in numerous studies to be the vascular endothelial cell (Bilsel et al., 1990, Thromb. Res.,

58:455-460), cytotropic actions have been shown for hepatic and myocardial cells as well (Lobel and Schror, 1985, Naunyn-Schmiedeberg's Arch. Pharmacol., 331:125-130).

Brief Summary Paragraph Right (6):
Defibrotide has been found to be a prostaglandin I.sub.2 (PgI.sub.2) secretory agent (Niada et al., 1982, Pharmacological Res. Comm., 14:949-957). Defibrotide also induces synthesis of other prostanoid metabolites, such as prostaglandin E.sub.2 (PgE.sub.2). The increase in secretion of the prostanoid metabolites, in particular PgI.sub.2 and PgE.sub.2, from vascular endothelial cells seems to involve interaction with arachidonic acid metabolites (Costantini et al., 1989, Eur. J. Int. Med., 1:115-120). It has been shown in rabbits that prostanoid neosynthesis induced directly by arachidonic acid was significantly enhanced by the stimulation of adenosine A.sub.1 and A.sub.2 receptors by defibrotide, especially at those levels that do not directly affect the output rate of PgI.sub.2 and PgE.sub.2 from the rabbit aorta vascular endothelial cells (Ulutin et al., International Scientific Symposium on Fibrinogen, Thrombosis, Coagulation and Fibrinolysis, Aug. 30-Sep. 1, 1989, Taipei, Taiwan, ROC). PgI.sub.2 and PgE.sub.2 promote microcirculatory vasodilation and antagonism of platelet aggregation. Defibrotide induces an in vivo increase in platelet cyclic adenosine monophosphate (cAMP) levels resulting in deaggregation of platelets and plasma prostanoid levels, as shown in humans (Cizmeci, 1986, Haemostasis, 16 (suppl. 1):31-35). Defibrotide does not increase levels of malonylaldehyde, thromboxane A.sub.2, thromboxane B.sub.2, .alpha..sub.2 -antiplasmin, or .alpha..sub.2 -macroglobulin activities.

Brief Summary Paragraph Right (7):
Defibrotide is also known to exhibit antithrombotic actions (Niada et al., 1981, Thromb. Res., 23:233-246). Defibrotide has been shown to elevate Protein CA and Protein CI levels, which affects antithrombotic action. The reported elevations in the levels of Protein CA and Protein CI are proposed to be via defibrotide's modulatory effects on the vascular endothelial cell-thrombomodulin levels. At the dose levels utilized thus far, it is devoid of anti-coagulant effects (Coccheri et al., 1982, Int. J. Clin. Pharm. Reg., 11(3):227-245), and no clinical applicability as an anti-coagulant agent has been taught heretofore.

Brief Summary Paragraph Right (8):
Defibrotide exhibits a synergistic action with, and potentiates the effect of heparin (Ulutin et al., International Scientific Symposium on Fibrinogen, Thrombosis, Coagulation and Fibrinolysis, Aug. 30-Sep. 1, 1989, Taipei, Taiwan, ROC). The synergistic mechanism between defibrotide and heparin is not totally clear. One proposed theory is that defibrotide competitively binds with heparin receptors, promoting prolonged circulation of endogenous heparin. Ulutin et al. reported an increase in anti-Factor Xa activity (Ulutin et al., International Scientific Symposium on Fibrinogen, Thrombosis, Coagulation and Fibrinolysis, Aug. 30-Sep. 1, 1989, Taipei, Taiwan, ROC). This effect may add to its antithrombotic action.

Brief Summary Paragraph Right (9):
In a comparable animal model of the rat aortic strip, defibrotide was shown to inhibit endothelin-induced contraction of the vascular smooth muscle (Fareed et al., 1990, In: Advances in vascular pathology, Elsevier Science Publishers B. V., pp. 171-177). This implies that factors other than impaired fibrinolysis were being treated by defibrotide, such as defibrotide-induced suppression in the levels of the vasoactive amines secreted from the vascular endothelial cells in response to injury. In umbilical vein human endothelial cell cultures, defibrotide was shown to increase cell number and protein content in the culture supernatant, implying a greater role in translation than in the induction of mitotic activity (Bilsel et al., 1990, Thromb. Res., 58:455-460).

Brief Summary Paragraph Right (10):
Additional data on defibrotide reveals that defibrotide can modulate lipid peroxidation of membrane phospholipids and oxygen radical induced inhibition of the cyclooxygenase pathway, two major mechanisms in the process of vascular endothelial cell injury. Analogous to these are defibrotide-induced inhibition of superoxide generation by neutrophils induced from platelet activating factor (PAF) (Cirillo et al., 1991, Haemostasis, 21:98-105). Defibrotide has shown protective effect in mice against pulmonary embolism, analogous to the free radical scavenging enzymes

superoxide dismutase and catalase (Niada et al., 1986, Haemostasis, 16 (suppl. 1): 18-25; Bonomini et al., 1985, Nephron, 40:195-200). Defibrotide-based antithrombotic action in pulmonary embolism may be analogous to the antioxidant effects of cardiovascular drugs.

Brief Summary Paragraph Right (11):
The cytotropic effects of defibrotide are proposed to be on the basis of PgI.sub.2 -induced vasodilatation of the microvasculature and the secondary increases in the tissue oxygenation and nutrition. While it has been reported that defibrotide acts via modulation of vascular endothelial cells, its recently formally adopted pharmaceutical classification as a "polypharmaceutical agent" is uniformly ascribed to defibrotide's PgI.sub.2 secretory action.

Brief Summary Paragraph Right (12):
Pre-clinical and clinical experience with defibrotide as well as ex vivo and animal studies done over the past ten years in Europe evidences a cyto-protective effect in myocardial warm and cold ischemia (increased tissue ATP, ADP, 2-3DPG, NADP/NADPH levels), and in reperfusion injuries in the ischemic myocardium and liver (decreased lactate, CPK, intracellular pH), as well as organ procurement and transplantation, proving its cyto-protective effects in other cell types such as myocardial and hepatic cells (Niada et aL, 1986, Haemostasis, 16 (suppl. 1): 18-25; Berti et al., 1990, Advances in Prostaglandin, Thromboxane, and Leukotriene Research, 21:939-942). The anti-ischemic effect-induced salvage of the cellular energy pools were ascribed to adenosine receptor induced stimulation of adenylate cyclase enzyme pathway.

Brief Summary Paragraph Right (13):
Defibrotide therapy has been used in disease states in which inappropriate production or intravascular deposition of fibrin has been a prominent factor. Peripheral obliterative vascular disease (POVD) comprises its primary commercial application in Europe (Ulutin, 1988, Semin. Thromb. Hemost., 14(suppl 1):58-63), accompanied by the secondary clinical indications of prophylaxis of perisurgical deep vein thrombosis (DVI), and by its less well established use in hemodialysis. Clinical application has been investigated in vasculitides (Raynaud's disease (humans)), prolongation of graft survival in renal transplantation (humans), DIC (animal models), sepsis (animal models), stroke (animal models), renal failure and thrombotic microangiopathy (HUS, TrP humans)) (Bonomini et al., 1985, Nephron, 40:195-200; Vangelista et al., 1986, Haemostasis 16 (suppl. 1):51-54; Oral et al., 1989, Blood 74(suppl 1):41 11a). Defibrotide has been administered to humans primarily as an investigational agent in the United States.

Brief Summary Paragraph Right (14):
Defibrotide is manufactured by CRINOS Farmacobiologica S.p.A., Villa Guardia (Como), Italy, and is currently marketed only in Italy. Defibrotide, obtained from CRINOS for investigational purposes and clinical trials in the United States, is available in ampules containing 200 milligrams for parenteral administration and in tablets containing 400 milligrams for oral administration.

Brief Summary Paragraph Right (15):
Although verifiable data indicates that defibrotide, as a nucleic acid, is not toxic, mutagenic or harmful to fetal or embryonic development, maximum dosages of defibrotide administered to humans have been limited to either a body weight-dependent dose of 10-30 milligrams per kilogram, to an empirically established dose of 5.6 grams per day, intravenously, or a fixed dose of 800 milligrams per day, intravenously or by mouth. Coccoheri and Biagi (Cardiovascular Drug Reviews, 1991, 9(2):172-196) report the highest dose of 2.4 to 5.6 grams daily which was given for three days only. These doses, which were based on previous animal studies, were administered empirically. Defibrotide was administered in conjunction with conventional therapy and produced modest advantage.

Brief Summary Paragraph Right (16):
The pharmacodynamic effect obtained with oral administration of defibrotide is approximately one-half that of parenteral dosing (Fareed et al., 1988, Seminars in Thrombosis and Hemostatis--Supplement, 14:27-37). The maximum dosages of oral defibrotide reported was 1600 milligrams per day. Even at these dosages, clinical improvement was much slower with the oral form of defibrotide than with the

parenteral form.

Brief Summary Paragraph Right (17):
Studies in human pharmacology have been conducted on the same nondynamic, merely descriptive, principles as the pre-clinical studies, i.e., merely confirming the molecular events induced by defibrotide at pre-determined, set dose levels, uniformly assessed on the principles of using a "minimum efficacious dose." In healthy volunteers, 1200 mg/2 hours was reported to induce increases in the levels of 6keto PgF.sub.1a and PgE.sub.2 (not confirmed subsequently by other investigators) (Gryzlewski R. J. et al., Eicosanoids, 1989, 2:163-167), and 1200 mg/day for 2 weeks induced production of prostanoids and inhibition of arachidonic acid 5-lipoxygenase products, the latter known to contribute to pathogenesis and evolution of ischemic tissue damage.

Brief Summary Paragraph Right (18):
The pro-fibrinolytic effect in healthy volunteers was confirmed by the administration of a single 400-600 mg dose with shortening only in euglobulin lysis time. Administration to peripheral obstructive vascular disease (POVD) patients in dose levels of 800 mg per day given orally, or 200, 400 and 800 mg per day given intramuscularly, displayed an additional effect of decreased PAI1 levels. Conversely, a more recent study failed to show significant activation of fibrinolysis in normal volunteers. A repeat study of POVD patients confirm significant defibrotide induced declines in PAI1 levels (Coccoheri and Biagi, 1991, Cardiovascular Drug Reviews, 9(2):172-196). As a whole, the fibrinolytic effects in healthy volunteers were in general not reproducible, but in patients fibrinolytic effects were reproducible.

Brief Summary Paragraph Right (19):
In direct opposition to its remarkable potentials in animal models and in vitro/ex vitro systems, published clinical studies with defibrotide have been notable for their modest-to-equivocal results in the respective areas of clinical application. One study continued intravenous defibrotide therapy for as long as three months ("Clinical Effectiveness of Defibrotide in Vaso-Occlusive Disorders and Its Mode of Actions", O. N. Ulutin, M.D. Thieme, Medical Publishers, Inc., Seminars in Thrombosis and Hemostasis--Supplement, Vol. 14, 1988). The majority of the remaining studies administered intravenous defibrotide for only two to three weeks, followed by the administration of oral defibrotide for a period of days to up to six months. Most studies ended at the discontinuation of defibrotide administration. Only one study followed patients for up to three years, although defibrotide was given for only three months ("Defibrotide: An Overview of Clinical, Pharmacology and Early Clinical Studies", Umberto Cornelli, M.D. and Marco Nazzari, M.D., Thieme Medical Publishers, Inc., Seminars in Thrombosis and Hemostasis--Supplement, Vol. 14, 1988). More recently, in a double-blind, randomized study conducted in peripheral arterial disease, defibrotide was administered orally for six months. Nearly all clinical studies (thus far) have focused on the agent's profibrinolytic and antithrombotic effects.

Brief Summary Paragraph Right (20):
In summary, defibrotide has been shown in the art to have antithrombotic, thrombolytic, cytotropic, nephroprotective, platelet deaggregatory and anti-shock properties. These properties have been ascribed to its capacity to release PgI.sub.2 or its stable analogues from vascular endothelium. Defibrotide has also been shown to increase t-PA, decrease PAI1, increase protein S and C levels, increase ATIII (unconfirmed reports), increase platelet cAMP levels and, more recently, decrease endothelin-I levels and increase EDRF (endothelium derived relaxing factor) in in vitro models.

Brief Summary Paragraph Right (21):
In all studies heretofore reported, a particular patient's condition was assessed by using the subjective and objective clinical signs and symptoms of the patient. To date, laboratory results, such as various coagulation assays have been used only to determine the safety and efficacy of defibrotide treatment but not to tailor the therapeutic dose to the individual patient's disease entity or the disease severity or response to prior treatment. Escalating dose levels were never attempted and/or evaluated. Rather, the art has assumed that side-effects will occur when defibrotide is administered in amounts exceeding the "minimum efficacious dose."

Brief Summary Paragraph Right (22):
Moreover, the art has not recognized that alkali salts of deoxyribonucleic acid, such as defibrotide, may be useful in the treatment of vial infections, including HIV infection.

Brief Summary Paragraph Right (29):
The invention provides a method of gene therapy which comprises administration of combinations of (1) sequence specific nucleic acids corresponding specifically to selected parts of the viral genome or transcriptional factors and (2) sequence non-specific nucleotides, such as defibrotide and analogues thereof, in incrementally higher dose levels in a marker dependent manner.

Brief Summary Paragraph Right (32):
The invention is directed to the universal treatment of disease states characterized by the compromise and/or absence of normal cell functions. Treatment with therapeutic nucleic acid compounds, such as defibrotide, is universal in its application with respect to any disease condition wherein the diseased cell preserves the biological capacity for the physiologically predefined events of the recovery process. The decisive factor in the success of this therapeutic approach is not only the pharmaceutical agent itself, but how it is utilized. Treatment in accordance with the invention results in the activation of the inherent reparative cellular activity which will lead to the reinstitution of normal cellular functions. Revival or restoration of normal cellular functions is, by definition, a state of cure.

Drawing Description Paragraph Right (2):
FIG. 2 is a graph showing normal peripheral blood cells labelled with 0, 10, 20 and 40 .mu.g defibrotide-biotin combination.

Drawing Description Paragraph Right (4):
FIG. 4 is a graph showing the lymphocyte uptake of defibrotide without biotin and labelled with Cy5.18.

Drawing Description Paragraph Right (5):
FIG. 5 is a graph showing the monocyte uptake of defibrotide without biotin and labelled with Cy5.18.

Drawing Description Paragraph Right (6):
FIG. 6 is a graph showing the granulocyte uptake of defibrotide without biotin and labelled with Cy5.18.

Drawing Description Paragraph Right (7):
FIG. 7 is a graph showing the percent expression of HIV viral proteins remaining when blood lymphocytes of an HIV infected individual were exposed to various doses of defibrotide with and without Con-A stimulation.

Drawing Description Paragraph Right (8):
FIG. 8 is a graph showing the laboratory response expressed in terms of mean linear fluorescence intensity of the peripheral blood mononuclear cells of an HIV infected individual, the cells being subjected in vitro to varying levels of defibrotide using a cell culture assay technique with and without Con-A stimulation.

Detailed Description Paragraph Right (1):
This invention provides a method for the therapeutic multiphase application of therapeutic compounds which are polydeoxyribonucleotides, oligodeoxyribonucleotides, and/or derivatives thereof, including but not restricted to defibrotide, in the treatment of disease states, including HIV. It has now been discovered that therapeutic nucleic acids such as defibrotide can be used in a manner not heretofore employed in the art to manage vascular, cardiac, renal, viral, autoimmune, inflammatory, and other disease states in which the reparative cellular mechanisms and modulation of cellular genomes are induced.

Detailed Description Paragraph Right (7):
It has now been discovered that the administration of sequence non-specific DNA, such as defibrotide, decreases IL-1, IL-2, TNF-.alpha. and IL-6, all of which are known

inducers of HIV proliferation. Administration of such an agent also increases total lymphocyte and T-lymphocyte counts, CD4 counts, and CD8 counts, as well as increasing cGMP/cAMP ratios to proportions seen in normal laboratory controls. An anabolic effect has also been observed.

Detailed Description Paragraph Right (12):
A system of dose assessment and completely new dose levels based on the concepts herein discussed has now been developed. First, since therapeutic nucleic acids such as defibrotide act to revive normal cell function, dose and duration of therapy must be modified individually per patient or disease depending on the function, type, and degree of cell injury. Second, defibrotide and other nucleic acids are cell modulators. In this regard, nucleic acids such as defibrotide and derivatives thereof have now been recognized by the inventor as the only class of agents committed to restoration of normal cell function. In itself, this effect of the therapeutic compound is incompatible (in a state of cure) with an "over-functional" state, i.e. any complications caused by the therapy. Hence, dose levels higher than the "minimum efficacious dose" used in the prior art will be complication free. Third, defibrotide has now been recognized to be a member of a new class of pharmaceutical agents that will act via activation of respective cell functions with varying polypharmacological actions that are disease specific, induced by varying dose levels of defibrotide. Fourth, this class of agents have to be administered at escalating dose levels until and when maximum clinical benefit is observed. Therapy with these agents requires the development of the "maximum efficacious dose" principle for the assessment of therapeutic dose levels, thus eliminating the heretofore universally applied principle of "minimum efficacious dose." Fifth, this class of agents represent the only polypharmaceutical agents of their kind which exert their therapeutic effects not by their direct molecular actions, but by activating (in the diseased cell) the selected polypharmacological events of the recovery process.

Detailed Description Paragraph Right (18):
The term "maximum tolerable dose," as used herein, is defined as the highest daily dose that can be administered without any complications, e.g., no bleeding complications or thrombopathy, etc. This in fact has been the sole and primary side effect of the high-molecular weight nucleic acid (defibrotide) utilized in the studies reported herein, i.e., the antithrombotic effect inducing bleeding complications at 300 mg/kg/day dose or above. If the maximum efficacious dose should be higher than the maximum tolerable dose, chemical modification of the nucleotide for more efficacious transmembrane transport and cellular entry would be necessary.

Detailed Description Paragraph Right (25):
Disease states involving cell malfunction of, for example, vascular endothelial cells, the cellular components of parenchymal tissue damage involving the kidney, heart, liver, etc., any disease state involving malfunctioning of the blood vessels, circulating blood cells, disease states of the central, peripheral and autonomic nervous systems and viral diseases involving reversible genetic modulation of the immune cells not excluding infestation of the tissue cells of the. involved organs may be treated with defibrotide and its derivatives. Such diseases include, but are not limited to POVD, DVT, DIC, thrombotic microangiopathies (e.g., HUS, TTP); renal failure; nephrogenic hypertension; consumptive thrombocytopenia, acquired thrombopathy and hemolysis; immunosuppression; autoimmune diseases such as rheumatoid arthritis; post-phlebitic syndrome; tissue necrosis with or without proximal vascular occlusion; acute/subacute (subendocardial) myocardial infarction; adult respiratory distress syndrome (ARDS); thrombosis of cranial sinuses; ischemic parenchymal tissue damage; acute myocardial infarction; pulmonary embolism; thrombotic cerebrovascular events; vascular endothelitis (e.g., Kawasaki's disease, polyarteritis nodosa, midline granuloma); scleroderma, Raynaud's disease; inflammatory (autoimmune or otherwise) myositis; inflammatory dermatitis; inflammatory symptoms of systemic lupus erythematosus (SLE) and other collagen vascular diseases; Sjogren's disease; inflammatory bowel disease (IBD); thyroiditis; stasis ulcers; sickle cell disease; pulmonary fibrosis; hypersensitivity pneumonitis; burns; peripheral obstructive arterial disease; septic shock; eclampsia; graft vs. host disease; retroviral diseases including HIV infection, adenoviral; herpetic and other viral infections; hyperimmune states such as chronic fatigue syndrome, solid organ rejection, venoocclusive disease, etc. Since prior art has shown the up-regulation of adenosine A.sub.1 and A.sub.2 receptors by defibrotide in the nerve cells, it can be inferred

that the prototype nucleotide defibrotide and its derivatives may also be therapeutically beneficial in treating diseases of the nervous system.

Detailed Description Paragraph Right (27):
The invention uses polypharmacological medical therapy components which are defined by the predetermined biological events of the cellular repair process. The invention defines a previously unidentified class of drugs whose pharmaceutical actions modulate selectively and most effectively the injury specific cellular functions. This class of drugs include defibrotide as well as other nucleic acid derivatives. The pharmaceutical action is guided by the intrinsic biological material of the cell matching specifically and completely the cellular events of the recovery to the exact components of the injury.

Detailed Description Paragraph Right (29):
The nucleic acid compound will preferably be relatively resistant to ecto- and endonucleases. The 3' OH of the terminal residue of the therapeutic compound according to this invention may be phosphorylated or not, and the compound will still function without the need for intracellular phosphorylation. The therapeutic compound according to this invention is a polyanion, and the negative charge is balanced by counter ions. The counter ions may be alkali metal ions or alkaline earth ions, biologic amines or other suitable counter ions which do not interfere with treatment according to the method of this invention. Preferably, at least some of the counter ions are zinc ions. Commercially available defibrotide contains about 150-350 .mu.g of zinc and about 25-45 .mu.g of iodine per gram of iodine. Zinc may be present in the nucleotide compound at a ratio of from 2-20 zinc atoms per phosphate group or iodine atom. Zinc containing compounds may be co-administered with the defibrotide to reach any desired ratio.

Detailed Description Paragraph Right (30):
Defibrotide is chemically characterized as a polyanionic derivative of deoxyribonucleic acid. While further discussion will be directed to the use of defibrotide as the prototype drug, it is to be understood that other nucleic acids and derivatives are included in the use thereof. Derivatives included within the scope of the invention include nucleic acid, i.e., DNA and/or RNA, which is conjugated with poly(L-lysine) or which is modified by, for example, the addition of amino acids such as lysine, histidine and arginine, the addition of optimum concentrations of folate and/or biotin, the addition of the optimum ratios of metals and ions including zinc, manganese and iodine, by the addition of 5'-polyallyl moieties, cholesterol, vitamin E, 1-2-di-O-hexadecyl-3-glyceryl and other lipophilic moieties and/or modified by the replacement of phosphodiester bonds with phosphothiotate bonds, and/or modified nucleotide sequences of the prototype nucleic acid, defibrotide.

Detailed Description Paragraph Right (31):
Verifications of the relative therapeutic unimportance of defibrotide's molecular structure in directly producing its various polypharmacological actions was provided by various means. These included non-uniformity of its various actions in different disease states; differences between the types of various "disease markers" reproducibly and effectively treated by defibrotide; lack of uniformity in the states of responsiveness of the same "disease markers" to the same "dose levels" at different stages of the disease process confirming greater responsiveness of the disease markers to lower dose levels with higher disease activity states and vice versa. This supports the concept that defibrotide's polypharmacological profile is a function of the injury state. The efficacy and the emergence of selected polypharmacological spectrum of actions, in turn, is a direct function of adequately administered dose levels.

Detailed Description Paragraph Right (32):
While the inventor does not wish to be bound to a particular theory with respect to the mechanism of action of defibrotide, it is believed that treatment with defibrotide leads to the direct modulation of second messenger molecules such as cAMP, cAMP dependent protein kinase A enzymes, adenylate cyclase, G-proteins, the modulation of balancing signal transduction systems of calcium and diacylglycerol pathway, phosphoinositol, and protein kinase C enzymes as well as to the modulation, via cAMP, of phosphoproteins of transcption and translation and cAMP modulated

oncogenes such as c-myc, ras, c-fos, c-jun, NK-KB, transcriptional factors and lymphokines such as EIAI, AP-1, COUP, IL-2, IL6, TCF-1.alpha., TATA, and TAT element, and oxygen radical modulation of cAMP response element (CRE) and modulation of CREB and CREM genes, as well as phosphoproteins of transcriptional and transitional cellular functions via protein kinase A/C induced phosphorylation of the respective enzymes.

Detailed Description Paragraph Right (33):
As shown by the data presented herein, derivatives of nucleic acids, such as defibrotide, act upon malfunctioning cells to restore normal cell function. For a given disease certain cell malfunctions may be caused by the disease while other cell functions are normal. Only the malfunctions of the cell will be affected by treatment with defibrotide. Normal functions will not be hindered and/or increased during treatment.

Detailed Description Paragraph Right (38):
Certain laboratory assays are used to assure that the dosages are safe for the patient being treated. For therapy with defibrotide these may include prothrombin time, activated partial prothromboplastin time, thrombin time, reptilase time, bleeding time, platelet function assays, and coagulation factors. A second set of laboratory assays (i.e., "disease markers") are utilized to indicate the efficacy of the doses. "Repair markers" are used to assess clinical adequacy of dose escalation and duration of therapy.

Detailed Description Paragraph Right (43):
Repair markers are compounds that participate in the regulatory pathways which include protein kinase A or protein kinase C. Adenylate cyclase is known to be activated by G-proteins (see Ross, 1992, Current Biology, 2(10):517-519, the disclosure of which is incorporated herein by reference) with eventual production of cAMP and cAMP-dependent activation of protein kinase A, leading to phosphorylation of the respective transcription factors, until 100% of the cell membrane receptors are taken up by the ligands. For defibrotide these receptors are .beta.-adrenergic receptors, collagen receptors, adenosine A.sub.1 /A.sub.2 receptors, ADP receptors, thrombin receptors, collagen receptors, etc). A parallel pathway operates through activation of protein kinase C, in response to intracellular calcium ion level, inositol triphosphate and diacylglycerol, responsive to ligand binding to another set of receptors and similarly controlling transcription/translation of respective proteins. These pathways, and their intermediate compounds are well known to those skilled in the art. In particular, "repair markers" are molecules in the pathways of the respective cellular repair processes defined by the type of injury. Repair markers are transcribed or shut off genes, second messengers and/or molecules of the signal transduction pathways that may be increased, decreased, or absent in response to cellular injury. As discussed herein, the term "repair marker" may refer to the compound or its concentration or the measurement value of an assay associated with the concentration of the compound. The level of a repair marker may deviate from the level present in the cell during normal function, and when it does so deviate, cellular repair processes are activated. This deviation may be positive or negative, depending on the disease state and the precise state of cellular repair currently in progress. As discussed herein, the "intensity" of the repair marker will refer to the degree of deviation from the level during normal cellular function, without regard to whether the deviation is positive or negative. The use of repair markers in establishing dose and duration of therapy is a novel mode of administering a pharmaceutical agent.

Detailed Description Paragraph Right (44):
As defined herein, a "universal marker" is a constitutively expressed molecule transcriptionally activated by the respective nucleic acid universally in all disease states for which the nucleic acid is specific. "Universal markers" are specific for each nucleic acid employed. While the universal marker is the only molecule that is not injury specific and has no therapeutic value, it is expressive of the event and duration of the ongoing repair process. Transcriptional activation gets shut off with the establishment of the state of cure. As such, the universal marker does not get modulated unless there is a disease state and the respective nucleic acid has therapeutic specificity. The universal marker carries a direct quantitative relationship to the daily per kilogram body weight dose (DKGD) of the nucleic acid

employed. The universal marker defined for the prototype nucleic acid (defibrotide) is vWAg. Other "housekeeping genes" related to particular nucleic acids can be selected as per the target cell involved from the respective "housekeeping genes."

Detailed Description Paragraph Right (53):
Initial administration of the selected dosage is followed by incrementally increasing dosages until the "maximum efficacious dose" is reached. A panel of laboratory assays to determine the state of the markers (e.g., absence, increase, decrease) is repeated every 3 to 7 days during therapy. These results together with the clinical markers of disease would indicate whether the defibrotide, or other nucleic acid derivative, is adequate in dose and duration to cause improvement in the pertinent marker or markers while simultaneously being totally safe to administer. Therapy is continued with escalating doses over sufficient time to assure complete normalization (i.e., the clinical laboratory assays, when compared to the reference range, are indicative of the normal condition) of the pertinent markers. When normalization is reached, therapy is stopped.

Detailed Description Paragraph Right (62):
A preferred embodiment of the treatment method applicable to all disease states treated according to this invention is diagramed in FIG. 1. An initial laboratory test panel (box 1) is first run which would consist of the respective set of "disease markers" and the universal panel of "repair markers" consisting of signal transduction/second messenger panel molecules. Additionally certain laboratory assays are used to assure that the dosages are safe for the patient being treated. For defibrotide these may include prothrombin time, activated partial prothromboplastin time, thrombin time, reptilase time, bleeding time, platelet function assays and coagulation factors (see baseline coagulation panel). "Disease markers" are utilized to indicate the overall therapeutic efficacy of the doses. These markers may be identified through blood tests, urine tests, clinical observation or identification of blood clots by any of several conventional techniques, or by the more refined techniques such as DNA fingerprinting and PCR. To evaluate the "disease markers" the laboratory analyses measure levels of certain proteins, lymphokines, enzymes and relevant molecules. Clinical markers may include blood pressure, visible tissue damage, signs of inflammation, ecchymoses, and the like.

Detailed Description Paragraph Right (63):
An initial bolus of defibrotide (box 2) is given intravenously over 15 to 30 minutes. Immediately thereafter the patient is given the daily dose of 40-400 mg/kg by continuous infusion. Preferably, the initial dose is a bolus (25-50 mg/kg) followed by 24-hour dose which is increased in 50 mg/kg/day increments every 1-3 days. The starting base-line dose may be from 40-400 mg/kg/day depending upon physician preference and the respective disease state treated. Lower initial doses are preferred for those therapeutic compounds which enter the cell nucleus more readily and are thus effective at lower doses. The bolus and daily dose for chemical derivatives of the nucleic acids may be calculated as a proportion of the defibrotide dose based on the relative cell-entry rate. It is preferred to administer this dose intravenously using two IV bags of 50 ml D5W, each bag infused over 12 hours. If for any reason the infusion is interrupted, the rate of infusion would be thereafter adjusted so that the patient will have received the calculated 12 hour dosage at the completion of the specified time period. This 24 hour dose range can also be administered in 2-4 bolus injections or per oral administration.

Detailed Description Paragraph Right (64):
Defibrotide or other selected nucleic acid derivative may be administered parenterally or orally. Parenteral administration is in the form of continuous intravenous infusion or intravenous bolus injection. Intravenous infusion may be accomplished by gravity feed, pump delivery or other clinically accepted methods. Oral administration may include the use of capsules, tablets or powders for any method of enteric administration.

Detailed Description Paragraph Right (65):
To permit clinically practicable administration of defibrotide in the amount necessary, materials for delivery of the agent optionally comprise 2.times.50 ml D5W IV bags each containing one-half of the calculated total 24 hour dose in milligrams of defibrotide, each bag infused over 12 hours for the IV-continuous infusion at the

maximum tolerable doses. Alternatively, the total 24-hour dose can be administered by bolus injection every 8-12 hours. The initial bolus injection and the subsequent outpatient bolus maintenance infusions are given, for example, in 3.times.25 ml D5W bags, each bolus to be infused over fifteen to thirty minutes. The oral dosage outpatient maintenance therapy in milligrams given daily (divided into 3-6 doses by mouth) would be the multiples of 2.times. the maximum tolerable IV dose.

Detailed Description Paragraph Right (66):
The same dose is given for three days and the laboratory test panel is repeated (box 3). A full coagulation profile and tests for markers should be run before and after any dose escalation. These tests results are compared with the initial test data to determine if any of the markers (which may include laboratory data or clinical observation for the disease being treated) have changed. A change is expected to occur in at least one marker within 3-21 days, indicating that defibrotide is having an effect. After each test the dose of defibrotide is increased by 50 mg/kg/day, dose for chemical derivatives being proportional to the cell entry rate for the respective nucleic acid, and continued at that dose for three days before retesting. This pattern of escalating the dose and repeating the laboratory panels is repeated (boxes 4 and 5) until the patient's "maximum tolerable dose" (MTD) is reached or until the disease/repair markers have plateaued or completely normalized.

Detailed Description Paragraph Right (67):
As evidenced by in vivo studies, it has been discovered that defibrotide, when administered to humans, decreases AgPAI1 (plasminogen activator inhibitor antigen) production and increases AgTPA production most efficiently starting at a dose range of 40-80 mg/kg/day, optimum effects being reached at 300-400 mg/kg/day dose range and above.

Detailed Description Paragraph Right (68):
It has also been discovered that defibrotide can be used as an alternate to, or as an adjunctive thrombolytic agent with t-PA, t-PA analogues, urokinases, streptolinases and their derivatives, when used in dose ranges of 300 mg/kg/day or above in the treatment of venous thrombosis and arterial thrombosis. In addition to being an adjunctive antithrombotic agent, defibrotide is also an effective adjunctive antiplatelet and cytotropic agent to t-PA, t-PA analogues, urokinases, streptokinases and their derivatives.

Detailed Description Paragraph Right (69):
Defibrotide is the drug of choice over aspirin as an adjunctive therapeutic agent to thrombolytic therapy at dose ranges starting at 40-80 mg/kg/day, most preferably 200 mg/kg/day and above. Defibrotide can also be used with vasopressin as an adjunctive therapeutic agent in thrombolytic therapy at dose ranges starting with 40-80 mg/kg/day, preferably 300-400 mg/kg/day or above. It is also the drug of choice over prostaglandins as agents that elevate cAMP levels to be used, as either adjunctive agents to thrombolytic therapy or antithrombotic therapy, or alone at dose ranges starting with 40-80 mg/kg/day, with optimum effects being obtained at 200 mg/kg/day and above. It is, likewise, the drug of choice, either alone or as an adjunctive, to agents that elevate cGMP at dose ranges starting with 40-80 mg/kg/day with optimum effects being obtained at 200 mg/kg/day and above.

Detailed Description Paragraph Right (70):
In diseases involving vascular endothelial cell, dose escalation should continue preferably until vWAg is greater than five times the initial baseline level. The upper limit may vary among the various derivative nucleic acids depending on their respective cell entry rates. For the prototype nucleotide, i.e., low molecular weight defibrotide, the safe upper limit is at least about 400 mg/kg/day and may reach 600 mg/kg/day. For the high molecular weight (45-50 kDA) defibrotide the sale upper limit is about 350 mg/kg/day. The dose ranges with the chemical derivatives of the nucleotide would correspond to dose ranges that elevate the base line vWAg antigen level to 5 times the initial value.

Detailed Description Paragraph Right (73):
The correct identification of markers are based on the identification of the pathways of disease pathogenesis and the respective repair processes and pathways. The mechanism of efficacy of the therapeutic nucleic acid simulate or are superimposed on

the cellular pathways of the respective repair process they induce. For example, using defibrotide as the clinical agent, one would (1) identify the known signal transduction systems and second messengers of the repair process, (2) define the most probable nucleic acid-induced repair markers of the known cellular repair pathway, and (3) define markers of the disease process related to disease pathogenesis.

Detailed Description Paragraph Right (74):
Many disease processes are pathogenically based on overactive body defense mechanisms. As such, a compound whose intracellular concentration can be a repair marker in one disease state can be a disease marker in another disease state. In such a case, the marker would usually be under-regulated by defibrotide instead of induced. Similarly, a marker of normal cellular function, if deficient, may be a disease marker. For example, the paralysis of cellular function of CD4 cells by the HIV retrovirus is secondary to the compromise of normal cellular markers of transduction pathways and second messengers.

Detailed Description Paragraph Right (75):
G-proteins instrumental in the activation of adenylyl cyclase are likely to be deficient in their active form with a low dose threshold level. In this case, the deficiency of the normal cellular marker of G-proteins would be a disease marker. Since defibrotide affects the adenylate cyclase pathway (increased cAMP by defibrotide), defibrotide would restore the second messenger of cAMP, which therefore would be a repair marker.

Detailed Description Paragraph Right (77):
When considered in conjunction with the published literature, the data reported herein demonstrates that defibrotide acts upon endothelial cells to revive an inadequate functional state of the normal cell. The first successful in vivo human pharmacological experiences of the effects of defibrotide on the inhibition of lipo-peroxidation and reversal of cyclooxygenase inhibition by the administration of correct dose level are shown herein.

Detailed Description Paragraph Right (78):
In addition to playing a role in the diseases discussed above, endothelial cells play a prominent role in heart disease, liver disease and kidney disease. Defibrotide has cyto-protective effects in myocardial cells and hepatic cells, as verified in patients with tissue necrosis; marker dependent doses of defibrotide can effectively treat these diseases. For heart disease, protein CA, protein CI and protein SI will be additional, yet optional, disease markers. Disease specific markers for liver diseases include SGOT, SGPT and GGPIT. Disease specific markers for kidney disease include creatinine, creatinine clearance, blood pressure, 24-hour urine volume, and 24-hour urine protein. vWAg and platelet aggregation by arachidonic acid will also be markers for these diseases.

Detailed Description Paragraph Right (79):
To increase second messenger markers of the above pathways, the maximum efficacious dose is the dose which will normalize the platelet aggregation assays, so as to established normal levels of 60-150% in all cases. Defibrotide and derivative nucleic acids are the first side-effect free platelet deaggregatory agents which induce this effect by restoring the integrity of the platelet functions (which by definition inhibit aggregation), and not by creating further defects in platelet functions like, for example, aspirin would. Hence this study shows the therapeutic nucleic acid to be the first proplatelet agent to be used within the arena of antiplatelet therapy.

Detailed Description Paragraph Right (82):
The studies reported herein support applicant's discovery that native defibrotide and chemical derivatives thereof are the pharmaceutical agents of choice in all the thrombotic disease states associated with the presence of a lupus anti-coagulant and other anti-phospholipid antibodies. Since elevation of the protein CA levels also involves activation of vitamin K via modulation of the redox state, the same levels are representative also for the nucleotide's actions at those levels involving lipid peroxidation, oxygen radical-induced injury states associated with impaired perfusion of organs or hypoxemia. Disease states involving the modulation of the anti-phospholipid antibodies include clinical states such as myocardial infarction, valvular cardiac lesions, glomerular tubular renal lesions, leak proteinuria,

nephrotic syndrome, skin and soft tissue necrosis, deep vein thrombosis, and post phlebitic syndrome related to the presence of lupus anti-coagulant and anti-phospholipid antibodies. The nucleic acid also induced complete disappearance of the circulating anti-phospholipid antibody for the duration of drug administration. Although the clinical beneficial effects were irreversibly established after cessation of drug administration, circulating anti-phospholipid antibody levels returned to abnormal values, albeit without any clinical abnormalities accompanying reappearance of circulating antibodies.

Detailed Description Paragraph Right (83):
Endothelin-I is constitutively released from the vascular and the endothelial cell, secretion of endothelin-I being regulated at the transcriptional/transitional level. Gene expression of endothelin-I depends on protein kinase C pathway which has been shown in this study to be suppressed by the prototype nucleotide, i.e., high molecular weight defibrotide. Hence, the dose level that suppress transcriptional/transitional activity involving protein kinase C pathway is also representative of the dose level at which the prototype nucleotide will be able to suppress or inhibit the protein kinase C pathway; including the receptor-ligand interaction, inhibition of inositol triphosphate and diacylglycerol and inhibition of release of Ca.sup.2+ intracellular levels. Action by this nucleotide has been qualitatively mentioned and shown in the prior art. However, doses representing the corresponding protein kinase C pathway inhibition have not been outlined in humans until this study. High molecular weight defibrotide will suppress endothelin-I levels starting at dose levels of 40-80 milligrams per kdlograms per day ideally at dose ranges of 160-200 milligram per kilogram per day or above. Dose levels of 275 mg/kg/day depress interleukin levels. High molecular weight defibrotide will furthermore balance activation of phosphoinositol/diacylglycerol signal transduction pathway also at the same dose levels.

Detailed Description Paragraph Right (84):
Preservation of .beta.-adrenergic receptor functions and prevention of .alpha.-adrenergic receptor overactivity by defibrotide has been described qualitatively in prior art animal models. However, human treatment doses starting at levels of 80-120 milligrams per kilogram per day, optimally seen at 160-200 milligrams per kilogram per day and above, have for the first time been used to treat humans. These doses have been deduced from the dose ranges arrived at via platelet aggregation studies.

Detailed Description Paragraph Right (87):
Injury-dependent increases in the PgE.sub.1 and 13-HODE molecules, requiring endothelial cell lesion are mirrored by defibrotide induced up-regulation of adenosine A.sub.1 and A.sub.2 receptors--which up-regulation is also an injury dependent event. Up-regulation of adenosine A1 and A.sub.2 receptors are inductive to generation of prostanoids, namely PgI.sub.2 which is converted into PgE.sub.1 by the injured endothelial cell. The present study has identified the only pharmaceutical agent thus far, namely defibrotide and derivatives thereof, that increase PgE.sub.1 generation as well as provision of 13-HODE, which are shown in the prior art to be the most important antithrombotic and platelet deaggregation molecules secreted by PMN. This is also in keeping with the showing that defibrotide will induce deaggregation of platelets as well as decrease the PMN numbers in the septic shock animal model. The pertinent markers for proplatelet effect are: intracellular Ca.sup.2+, intracellular cAMP, platelet factor 4, platelet .beta.-TG, glycoprotein 1b, collagen/arachidonic acid stimulated ATP secretion by platelets, platelet activating factor (PAF), 6keto PgE.sub.1 (PgI.sub.2 metabolite in plasma), 6-keto PgI.sub.1.alpha. (PgI.sub.2 metabolite in plasma), 13-HODE (PMN), 5-HETE (PMN), 6 PgE 1/5 HETE ratio. (Intracellular calcium level is routinely measured by Quin-2 method). NADPH oxidase exists in some membranes of inflammatory phagocytes. Prior art has shown increased NADP ratio with the prototype nucleotide defibrotide.

Detailed Description Paragraph Right (89):
The prototype high molecular weight defibrotide, native defibrotide, low molecular weight native defibrotide, and chemical defibrotide derivatives regulate genes which are regulated by cAMP. These genes include vasoactive intestinal peptide (VIP), somatostatin, human chorionic gonadotropin, phosphoenolpyruvate carboxylkinase, tyrosine hydroxylase, fibronectin, prolactin, ornithine decarboxylase, interleukin-6

gene, c-fos oncogene, haptoglobin, hemopexin, C-reactive protein (CRP), as well as other cellular genes which are regulated by cAMP responsive element (CRE), transcriptional factors interacting with CREB (which is 43 kd protein that interacts with CRE via leucine zipper, such as c-myc products, c-fos products, ATP (Activating Protein), SRE (serum responsive element), API. Protein kinase A will activate endogenous CREB activity and will also enhance viral transactivation. CRE/CREB related transcription of genes including HIV Long Terminal Repeat (LTR) will be positively induced with high cAMP levels.

Detailed Description Paragraph Right (90):
The selected nucleic acid, e.g., defibrotide, will affect only injury-dependent parameters in each individual patient. As such, no uniform action will be observable in all patients. For the nucleotide transcriptionally-activated parameters, analysis is made for the highest values in each dose range. For the nucleotide transcriptionally shutoff parameters, analysis is made for the lowest value in each dose range.

Detailed Description Paragraph Right (91):
Several prototype markers have now been shown to reflect transcriptional genomic activity by nucleotides which increase cAMP, adenylate cyclase via the interaction of G-proteins, and phosphorylate transcriptional factors via protein kinase A. These markers are vWAg, AgTPA and .beta..sub.2 -microglobulin. While vWAg and AgTPA are representative markers, any molecules which are initiated by nucleotides, or derivatives such as defibrotide, to induce transcriptional activity are included.

Detailed Description Paragraph Right (92):
It has been discovered that vWAg may be employed as a universal marker to guide the assessment of the duration of therapy, i.e., the most therapeutic dose, as well as the most efficacious daily dose. It has been discovered, as reported herein, that vWAg is transcriptionally activated by defibrotide irrespective of the type of injury. Analysis of patient data has led to the unexpected finding that with the onset of cure, vWAg levels decline. The production of vWAg will be activated by defibrotide only for the duration of the injury and the repair process. In this regard, defibrotide will not effect vWAg levels in healthy individuals or following the establishment of cure, i.e., vWAg level will decline to baseline regardless of ongoing therapy. Concurrent analysis of vWAg with various "disease markers" correlated with changes in the disease marker levels. In other words, it has been discovered that therapy dependent absolute changes in disease markers (decline or increase) correlate with peak vWAg levels. The normalization of disease markers, in turn, correlates with decline in vWAg levels.

Detailed Description Paragraph Right (93):
von Willebrandt antigen (vWAg) is classified according to this invention as being a universal dose marker. vWAg can be utilize as the universal marker for all nucleotides that induce activation of cAMP and protein kinase A enzymes. vWAg is a plasma glycoprotein having a molecular weight of approximately 200,000 which is constitutively secreted by the endothelial cell. It is important in hemostasis as a prothrombotic factor (factor VIII/vWAg protein) and as an inducer of adherence of platelets to the exposed subendothelium. In every disease state, vWAg levels go up with increasing defibrotide dose levels when the dose is adequate to stimulate vascular endothelial function.

Detailed Description Paragraph Right (94):
In accordance with the invention, an increase in the vWAg level corresponds to the induction of transcriptional activity of this gene by the nucleic acid. Elevation of vWAg is representative of the ongoing repair process. The decline in the level and eventual normalization of vWAg during therapy is representative of the cure process. Plateau in the level of vWAg correlates with the application of the maximum efficacious dose. Without exception, the elevation in the level of vWAg is concurrent with modulation of the disease marker and activation of the repair marker. Here the maximum efficacious dose is determined along with vWAg, so as to normalize the levels of these molecules between 65-150%, and eliminate the intracellular oxygen radicals (measured by chemiluminescence, normal state being negative). For the prototype drug, defibrotide, the maximum efficacy in inducing transcriptional activation of vWAg occurs at doses of 40 DKGD and above, ideally within the DKGD range of 40-400. The

universal marker vWAg dose levels are representative dose levels by the prototype's transcriptional/transitional modulatory effects. Fitting the definition of universal marker, vWAg does not contribute to the expected correction of bleeding time but acts as a functionally dormant molecule.

Detailed Description Paragraph Right (97):
While platelet aggregation with arachidonic acid, ADP 20, ADP 10, ADP 5 and collagen also are therapy increasing markers, they are not representative markers for the transcriptional activity of the nucleotide. Rather, they constitute markers for the various receptors the corresponding statistics of which are to be interpreted as for vWAg and AgTPA. The dose ranges are representative of the dose ranges affecting receptor ligand interactions as well as stimulation of prostanoid secretion by the prototype nucleotide, since prior art has shown that defibrotide up-regulates Adenosine A.sub.1 and Adenosine A.sub.2 receptors (represented in this work by the up-regulation/normalization of the arachidonic acid and ADP induced platelet aggregations). Prior art also has shown that up-regulation of Adenosine A.sub.1 and Adenosine A.sub.2 receptors is inductive of up-regulation of PgI.sub.2 secretion, independent of cyclooxygenase/arachidonic acid pathway. In this study for the prototype (defibrotide) up-regulation of Adenosine A.sub.1 and A.sub.2 receptors and cyclooxygenase pathway-independent secretion of prostanoids occur optimally at dose levels of 120-200 mg/kg/day, the effect starting at dose levels of 40-80 mg/kg/day. These constitute also the optimal dose levels for the "pro-platelet" effect of defibrotide. While projected dose-levels indicate beyond 400 mg/kg/day the added benefits may be negligible, these higher dose levels are to be considered for the low molecular weight native defibrotide. For the chemical derivatives with varying degrees of cell-entry the optimal dosages would be corresponding to dosages increasing vWAg levels to 5.times.the baseline.

Detailed Description Paragraph Right (98):
Hence analogous to the induction of top transcriptional activity, induction of the optimum receptor/ligand interaction would also require that the vWAg level be raised 5 times (or 500%) and cAMP to 100% of the baseline levels, respectively, since 100% occupation of epinephrine/norepinephrine receptors (prototype receptor/ligand interaction for defibrotide and derivative nucleotides) would translate into 100% increase in intracellular levels of cAMP via activation of adenyl cyclase enzyme. To induce the cell at the top performance level in either shutting off or turning on of the repair molecules, the maximum efficacious dose has to be increased to reach these numerical values. In turn the maximum therapeutic dose is determined by when the vWAg and/or intracellular cAMP levels decline to baseline levels during therapy with maximum efficacious dose.

Detailed Description Paragraph Right (111):
It has now been discovered that the administration of non-sequence specific DNA, such as defibrotide decreases Il-1, Il-2, TNF-.alpha. and Il-6, all of which are known inducer of HIV proliferation. Administration of such an agent also increases total lymphocyte and T-lymphocyte counts, CD4 counts, and CD8 counts, as well as increasing cGMP/cAMP ratios. An anabolic effect has also been observed.

Detailed Description Paragraph Right (112):
Defibrotide's mechanism of efficacy relates to modulation of cell functions at the nuclear genomic level through one or more pathways by modulation of the cell's genetic material, i.e., DNA itself or translation or transcription of the genetic information. Defibrotide-induced cellular modulation restores the normal functions of the cell such as the production of normal proteins needed by the cell and, in the case of HIV, the correction of the effects of the abnormal, viral encoded genetic material by inhibiting its further production at the expense of the normal, virus-free genetic material. In the course of the multiphase treatment, defibrotide is administered at dosages much greater than previously described in the literature. Preferably, in treating HIV, an initial bolus dose of 100 mg/kg in 50 ml DSW is infused over a period of 30-60 minutes followed by 200 mg/kg/day infused in 250-500 ml DSW over a period of 3-24 hours. From day 2, dose is escalated to maximum tolerable dose, maximum efficacious dose and maximum therapeutic dose levels. The dosages and durations of the phases of therapy are adjusted according to the results of laboratory studies performed on the patient's infected cells. In this way, the HIV virus may be inactivated and its proliferation arrested. Therefore, the progress of

the disease may be arrested or ameliorated.

Detailed Description Paragraph Right (113):
Because HIV virus adversely affects the genetic material and function of the cells, defibrotide can effectively treat HIV infection as long as the carrier CD4.sup.+ cell and/or the monocyte harboring the virus preserves the physiological ability to revive itself. Therapeutic success with defibrotide, however, is strictly dependent upon the assessment of the correct treatment doses for the respective disease states. Moreover, since the optimum function of the normal cell, by definition, would not be compatible with any complications, defibrotide at any defined maximum efficacious dose, specific for any patient and disease state would be complication-free.

Detailed Description Paragraph Right (115):
Efficacy of defibrotide may have several concurrently active mechanisms. Defibrotide may provide anti-sense neutralization of the viral proteins. Defibrotide's mechanism of efficacy may be at the nuclear level by modulation of genetic functions via other pathways as well. Defibrotide's actions may be more apparent during viral phases which involve translation and/or transcription of the DNA message, so as to revive the normal function of the cell at the expense of the disease-specific molecules. This action may be analogous to anti-viral effects of Ampligen (a mismatched double stranded RNA-molecule. However, whereas Ampligen exhibits immunostimulating effects, agents such as defibrotide are both immunostimulants and immunosuppressants. Defibrotide may modulate viral penetration into the cell via its known action of inhibiting intracellular calcium mobilization. Also, defibrotide may directly inhibit viral enzyme reverse transcriptase via inducing ATP production analogous to ddl (dedeoxyinosine), by virtue of its known action of inducing high energy metabolites (ATP, ADP, NADP/NADPH), possibly via modulation of Complex-I respiratory molecule. Defibrotide may inhibit protein kinase C analogous to Hypericin. Additionally, defibrotide decreases Tissue Necrosis Factor (TNF), a cytokine known to promote HIV-I activation, by its known effect on increasing cAMP levels at the correct defibrotide dose level.

Detailed Description Paragraph Right (116):
Whatever the mechanism, zinc is known to have an inhibitory effect upon nucleases acting on phosphodiester linkages, as well as an enhancing effect on base pairing. U.S. Pat. No. 3,770,720, teaches that in the production of defibrotide, zinc should be removed from the molecule. However, in the treatment of AIDS, it is preferred that zinc be present. Moreover, it is preferred that iodine should also be present. In the defibrotide used in the Examples iodine was present in an approximate ratio of one zinc atom per iodine atom and a two to one ratio of zinc+iodine to nucleotide base.

Detailed Description Paragraph Right (117):
As can be seen from comparing the cellular uptake data shown in FIGS. 2 and 3 with the data shown in FIGS. 4, 5 and 6, a greater level of defibrotide enters the lymphocytes when biotin is present. Horn et al. (Plant Physiol, 1990, 93:1492-1496) has observed that biotinylated molecules enter the cell via the folate endocytic pathway. The data of FIGS. 2-6 read in conjunction with the above-cited Horn reference, indicate that defibrotide with biotin may also use the folate endocytic pathway.

Detailed Description Paragraph Right (118):
Defibrotide may jointly and/or selectively modulate one or several pathways. This modulation will be, only to the appropriate degree thus surpassing all of the other anti-HIV agents in its lack of side effects, yet presence of proven efficacy. Defibrotide will achieve this result only when the dose levels are tailored to the patient, stage of disease activity and/or reigning stage of viral activity.

Detailed Description Paragraph Right (120):
The method of treating the HIV-infected patient begins with a panel of laboratory studies which include the quantitative evaluation of the activated peripheral blood mononuclear cell subsets, circulating viral proteins, cytokinases and soluble cell-surface receptors. The initial administration of a selected dosage of defibrotide is followed by incrementally increasing the dosage of defibrotide until a maximum tolerable dose is reached. The laboratory panel is repeated weekly during this therapy. These results together with the clinical markers of disease would

indicate whether the defibrotide is efficacious and whether defibrotide should be continued to be given alone or with other therapeutic agents.

Detailed Description Paragraph Right (125):
Gene therapy has not, heretofore, been tried without the interaction of viral vectors, i.e., by the administration of nucleic acid-based pharmaceutical agents orally and/or by intravenous route. The prototype drug defibrotide, although administered to patients over the past 5-6 years, has never heretofore been contemplated for gene therapy. In addition, in other modalities of gene therapy, dosage has never been assessed by molecule markers. Molecule markers have never been defined within the system of secondary messengers, signal transduction systems, promoters (DNA sites which are on the same chromosome as the gene transcribed and to which RNA polymerase binds), enhancers (DNA regions that control a promotor from a great distance, sometimes as much as 30,000 bases), and transcription factors (diffusible regulatory proteins which bind to DNA transcription activation domains and regulate the rate of transcription by RNA polymerase).

Detailed Description Paragraph Right (136):
It has now been discovered that the co-administration of various anti-sense or missense nucleic acids with, for example, defibrotide, would (1) alleviate the complication of cAMP induced viral replication; (2) induce inhibition of viral replication mediated via modulations of cAMP, protein kinase A, protein kinase C, cellular redox state, G-proteins, or cAMP induced gene promoters (in this regard, defibrotide and other nucleotide derivatives introduce for the first time into anti-HIV therapy nucleotides with no sequence specificity that concurrently modulate the totality of the cellular second messenger/signal systems for rapidly transducing extracellular signals into specific patterns of gene expression in the nucleus); (3) concurrently induce inhibition of viral replication with sense, anti-sense, or missense nucleic acids (e.g., DNA, mRNA, DNA/RNA ribosomes, inhibitors of viral protease, viral integrase); and (4) introduce a modality of gene therapy (i.e., genetic engineering) which can be safely administered to humans, which does not utilize viral vectors, which can be administered either intravenous or orally, which enables administration of sequence specific combination of nucleic acids adjusted specifically to the selected parts of the HIV-genome and cellular repair pathways, which adjust the dose so as to modulate selected genes or cellular/viral molecules, which enables the most efficient administration of various different nucleotides with differing cellular uptake dynamics and chemical anti-viral potencies, and which administers excess DNA to enable the self-integration of DNA.

Detailed Description Paragraph Right (138):
Combination nucleic acids will, hereinafter, be referred to as "combo-nucleic acids". Combination of sequence nonspecific prototype nucleic acids (e.g., defibrotide and derivatives thereof) with various sequence specific nucleotides has never, heretofore, been proposed for use as a multimodal therapy for HIV.

Detailed Description Paragraph Right (143):
To measure the effect of defibrotide on HIV it was first necessary to label the drug and determine whether defibrotide will enter the nucleus of the human cell. Knowing the phosphodiester linkages in defibrotide, its comparative nuclear penetration was assessed by labelling defibrotide with a photo-activatable analogue of biotin. The biological activity of defibrotide after labelling was considered to have been preserved since published data shows that previous oligonucleotide probes have been labelled with conjugates and still remained biologically active. Image analysis utilizing a cold CCD camera revealed that uptake of defibrotide was localized in the nucleus. This supports the hypothesis that the mechanism of efficacy for defibrotide is largely contributed to by its modulatory activity on the genetic material of the cell, no matter what disease entity is being treated. As shown in FIGS. 2 and 3, the nuclear uptake of defibrotide is directly proportional to the concentration of defibrotide with biotin. The observed uptake supported the increased efficacy of defibrotide with the larger doses used, and also supports the hypothesis that at critically high dose levels various previously unknown different effects of defibrotide can be seen. It was also observed that uptake by monocytes was significantly greater than that by lymphocytes.

Detailed Description Paragraph Right (144):

The cellular uptake of defibrotide without biotin and labelled with cyanine dye Cy5. 18 was also measured. It was observed that biotinylation of defibrotide enhanced the cellular uptake of defibrotide in the lymphocyte population. However, there was no difference in uptake between monocytes incubated with biotinylated or fluorescently tagged defibrotide. This can be seen by comparing FIGS. 4 and 5.

Detailed Description Paragraph Right (145):
To further confirm the specificity of defibrotide for the treatment of HIV infection, HIV infected peripheral blood mononuclear cells with varying doses of defibrotide were evaluated by staining for all viral envelope proteins using concanavalin A (Con-A) stimulated and unstimulated cells (Anti-HIV 1, and Anti-HIV 3 specific Anti-HIV antibody). The blood sample was obtained from a patient using an evacuated blood collection tube containing sufficient EDTA to prevent coagulation of the sample.

Detailed Description Paragraph Right (148):
Subpopulations of unstimulated and stimulated white cells were then incubated in the presence of discrete concentrations of defibrotide. Each successive assay employed successively greater concentrations. A control sample of incubate containing no defibrotide was also prepared. A labelling antibody solution was prepared by directly conjugating Cy5. 18 with human .alpha.-HIV antibody to a final dye/protein ratio of 5.0 (.alpha.-HIV-Cy5.18).

Detailed Description Paragraph Right (152):
FIG. 7 shows HIV protein expression at selected dosages. Assay results for the same sample shown in FIG. 8 are in terms of the intensity of the fluorescence of certain antibody-labelled mononuclear leukocytes (Mean Linear Fluorescence Intensity). Fluorescence intensity is proportional to HIV protein expression, and thus the activity of HIV. It is seen that the expression of the HIV proteins decreases and then levels off with increasing concentrations of defibrotide.

Detailed Description Paragraph Right (153):
Before administration of defibrotide, Con-A stimulated cells expressed 32% more viral proteins. However, after administration of 20 mg of defibrotide, both stimulated and unstimulated cells express 70% less viral proteins. At 30 mg concentration of defibrotide in both Con-A stimulated and unstimulated cells the expression of viral proteins leveled off. This supports the specificity of defibrotide for HIV-virus as well as the fact that if cells are induced to divide, translating into proliferation of the virus, more HIV virus can be killed, albeit, at higher doses.

Detailed Description Paragraph Right (154):
Patients with various diseases of vascular prothrombotic backgrounds were treated with escalating dose levels of defibrotide. A variety of coagulation and hematological assays with other molecular markers of inflammation, etc., were conducted on blood samples drawn from the patient before and after each dose escalation. From an analysis of the test results and clinical observations, it was discovered that certain effects of defibrotide lead to a remission state of certain specific aspects of disease states corresponding to the various dose ranges employed.

Detailed Description Paragraph Right (155):
As an example, hematological recovery in thrombotic microangiopathy, generally, yet not exclusively, occurred when the patient received doses of defibrotide ranging from 20 to 30 mg/kg/day. These doses however did not cure the renal lesions since creatinine levels remained above normal (or only partially corrected) at the dose levels where hematological recovery was complete. Renal recovery evidenced by normalization of creatinine levels occurred between 40 and 250 mg/kg/day.

Detailed Description Paragraph Right (156):
Even in the presence of normalization of creatinine levels (the conventional criteria of complete recovery) it was observed that complete remission was yet to be reached by the observation of elevation of blood pressure, low AgTPA and high fPAI levels. Therefore, doses of defibrotide continued to be increased until blood pressure levels became normal. The dose elevation not only treated blood pressure, but also led to further improvement of creatinine. Thus, treatment with marker-dependent doses,

applied correctly, led to a state of "cure".

Detailed Description Paragraph Right (157):
In a normal individual, it was determined that increasing the DKGD dose does not induce any elevation in the vWAg since there is no ongoing repair process, i.e., no disease state. Doses administered to a normal individual, in contrast to the doses given to an individual exhibiting a pathological disease state, will not induce any alteration in vWAg levels, i.e., defibrotide will not induce transcriptional activity at the genomic level. vWAg predicts the transcriptional rate of the respective repair molecules induced by the nucleotide and will guide the assessment of maximum efficacious dose and maximum therapeutic dose.

Detailed Description Paragraph Right (158):
The minimum value of the vWAg level among a group of disease patients ("minimum highest value") was monitored when defibrotide was administered at a daily dose within the range of 10-400 mg defibrotide/kg/day (DKGD). Each increase in DKGD increases the preceding minimum highest value of vWAg by an increment smaller in each successive interval. Using defibrodde, the highest percentages of increments were found to occur at the borderline of 40 DKGD. Increasing DKGD above 400 induces only negligible improvements over levels below this dose. In practice, this is the dose level above which complications of bleeding have been observed by the inventor with high molecular weight defibrotide.

Detailed Description Paragraph Right (161):
Examples 5-7 report the treatment of three HIV infected patients. These patients were all treated in Turkey with defibrotide obtained from CRINOS. In Tables I-VI, below, the following are the normal laboratory ranges: IL-1=3.6 pg; IL-2=4.3-4.8 pg; IL-6=7.1-7.3 pg; TNF.alpha.=25.1-26.3 pg; cAMP=0.4-0.6 nM; CGMP=0.85-0.95 nM; normal cGMP/cAMP=2.125; .beta..sub.2 -microglobulin=<1900 .mu.g/l.

Detailed Description Paragraph Right (162):
A 28-year old white HIV.sup.+ /ARC male exhibiting waste syndrome, Herpes labialis and Herpes genitalis associated with widespread tissue damage, oral/pharyngeal candidiasis, polyarthralgias and tuberculosis was treated with defibrotide.

Detailed Description Paragraph Right (163):
On Day 1 of treatment, a 360 mg/kg IV bolus of defibrotide was administered. Thereafter, a dose of 160-275 mg/kg/day was administered. Defibrotide was administered 86 days out of a 118 day treatment course.

Detailed Description Paragraph Right (166):
The effect on Herpes began on day 4 of treatment. By day 36 of the treatment period, genital Herpes lesions were in complete remission. By day 68, Herpes labialis lesions were in complete remission. No relapses were seen with temporary cessation of defibrotide.

Detailed Description Paragraph Right (170):
25-year old white HIV.sup.+ female was treated with defibrotide. At the onset of therapy, the patient was asymptomatic but had a low CD4 count.

Detailed Description Paragraph Right (171):
On day 1 of the treatment, a 200 mg/kg IV bolus of defibrotide was administered. Thereafter a dose of 150-275 mg/kg/day was administered. Anabolic effects of the DNA were seen by day 13.

Detailed Description Paragraph Right (180):
The best and most efficacious clinical application of defibrotide and other polynucleotides is as pharmaceutical cell modulators committed to revival of normal cell function. The doses and the markers will vary among diseases. Moreover, the markers for any given disease will frequently vary among different stages of the disease. The aim of treatment is the irreversible normalization of a marker or markers. Once this is obtained, a subsequent marker for the lower disease activity will be sought and treated. The possibility of cure depends on the identification of appropriate markers. The selection and use of markers to determine doses can be best understood with reference to selected patient data presented hereafter as

representative examples of patients suffering from thrombotic microangiopathy (HUS), prothrombotic states of neoplastic chemotherapy induced or immunological (anti-phospholipid antibody) etiologies, deep vein thrombosis, and soft tissue necrosis, as well as acquired platelet function abnormalities. Incidental therapeutic effects of defibrotide in these patients also involved pulmonary (e.g., adult respiratory distress syndrome (ARDS)), cardiac (e.g., subendocardial myocardial infarction) and renal systems (e.g., glomerular proteinuria). There is an optimum level of transcriptional activity induced that is specific for each patient. This level depends on maximum efficacious dose, acuteness and degree of injury, and specificity of the nucleotide for the treatment.

Detailed Description Paragraph Right (181):
The pathological states exhibited prior to therapy of patients Nos. 4-14, as well as the condition exhibited following therapy, are summarized below. All patients treated were resilient to conventional therapy and considered to be, at the time of treatment with defibrotide, moribund.

Detailed Description Paragraph Right (198):
The initially normal level of TNF was elevated between days 28-38. This period was concurrent with the development of acute respiratory distress syndrome and myocardial infarction with conduction defect cell lesion. Noted are clear, inverse relationship of increasing vWAg levels with declining AgPAI1, and endothelin-I levels, a repeatedly observed phenomenon governing the behavior of vWAg with the modulation of any disease marker in either direction in any one patient. Decline in AgPAI1 shows it to be a representative marker of endothelial cell injury/repair phenomenon rather than a marker of effective fibrinolysis, since its behavior is not accompanied by increasing AgTPA levels. Furthermore this patient did not display any increased fibrinolytic activity with reference to the dissolution of various thrombi in his vasculature. As in Patient No. 5, at the time of the most extensive and acute lesion, transcriptional/transitional modulatory repair event by the nucleotide was at its peak, represented universally in the transcriptional modulation of vWAg. On no other chemical therapy, but only on defibrotide, ARDS lung findings and subendocardial myocardial infarction enzyme and electrocardiogram findings completely reversed by day 51, accompanied by the precipitous drops in AgPAI1, and endothelin-I, levels both molecules being disease markers for any type of endothelial mitral valve prolapse and ventricular wall dysfunction (documented by EKG and echocardiograms). These events occurred between days 35-38 while off therapy with defibrotide. The events were etiologically/temporally related to infusion of streptokinase. Nucleotide therapy was reinitiated at 60 mg/kg/day dose (day 38) escalated to 80 mg/kg/day dose (days 38-41), followed by 100 mg/kg/day dose (days 41-50), decreased to 80 mg/kg/day dose (days 50-53), and finally completely discontinued from day 53 on. Follow-up without therapy was until day 275.

Detailed Description Paragraph Right (200):
This patient showed therapeutically successful human doses of defibrotide in the modulation of redox-state, NADP/NADPH, FAD/FADH.sub.2 oxidative phosphorylation pathway, the so-called "cytotropic" action of the drug. The clinical corresponding pictures of soft-tissue necrosis and deep vein thrombosis as well as post-phlebitic syndrome were irreversibly, completely cured.

Detailed Description Paragraph Left (17):
Method of Treating HIV-Infected Patients with Defibrotide

Detailed Description Paragraph Type 1 (119):
a) defibrotide sequence+TAR decoy RNA,

Detailed Description Paragraph Type 1 (120):
b) defibrotide sequence+negative mutants of the viral REV transactivator,

Detailed Description Paragraph Type 1 (121):
c) defibrotide sequence+synthetic promoters with the consensus sequence for binding of the transcription factor Sp1, and the TATA box,

Detailed Description Paragraph Type 1 (122):
d) defibrotide sequence+TAT mutants, mutations involving the seven cysteine residues,

Detailed Description Paragraph Type 1 (123):
e) defibrotide sequence+sense derivatives of CIS acting negative elements (CRS) present in the integrase gene+REV mutants,

Detailed Description Paragraph Type 1 (124):
f) defibrotide sequence+transdominant suppressor of REV (mutations involving amino acid 78 and 79),

Detailed Description Paragraph Type 1 (125):
g) defibrotide sequence+NEF-cDNA sequence with or without U3 region sequence of the 3'LTR,

Detailed Description Paragraph Type 1 (126):
h) defibrotide sequence+POL reverse transcriptase gene mutants,

Detailed Description Paragraph Type 1 (127):
i) defibrotide sequence+POL viral integrase gene mutant,

Detailed Description Paragraph Type 1 (128):
j) defibrotide sequence+POL viral protease gene mutant,

Detailed Description Paragraph Type 1 (129):
k) defibrotide sequence+HIV-I LTR enhancer (-137 to -17) mutant,

Detailed Description Paragraph Type 1 (130):
l) defibrotide sequence+HIV-I LTR sense sequence of the negative regulatory element (-340 to -185),

Detailed Description Paragraph Type 1 (131):
m) defibrotide sequence+LTR NFKB mutant (-104 to -80),

Detailed Description Paragraph Type 1 (132):
n) defibrotide sequence+LTR Spp1 (GC box) binding site and TATA box mutants,

Detailed Description Paragraph Type 1 (133):
o) defibrotide sequence+LTR GAG gene sequence mutants,

Detailed Description Paragraph Type 1 (134):
p) defibrotide sequence+ENV, GAG, POL gene sequences placed 3' of the REV mutant codon, and

Detailed Description Paragraph Type 1 (135):
q) defibrotide sequence+host DNA sequence of preferred targets for proviral integration.

Other Reference Publication (4):
Ferro, "Possible Enhancement of Endothelial Cell Function Induced by Defibrotide," Chemical Abstract (1988), 109:104533m.

Other Reference Publication (7):
Marni, "Protection of Kidney from Postischemic Reperfusion Injury in Rats Treated with Defibrotide," Chemical Abstract (1991), 114:55511v.

Other Reference Publication (8):
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Bonomini, et al., "Effect of a New Antithrombotic Agent (Defibrotide) in Acute Renal Failure Due to Thrombotic Microangiopathy," Nephron, 40:195-200 (1985).

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Other Reference Publication (18):
Cizmeci, et al, "In vivo Effects of Defibrotide on Platelet c-AMP and Blood Prostanoid Levels," Haemostasis, 16:31-35 (1986).

Other Reference Publication (19):
Coccheri, et al., "Effect on Fibronolysis of a New Antithrombotic Agent: Fraction P (Defibrotide). A Multicentre Trial," Int. J. Clin. Pharm. Res., 11:227-245 (1982).

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Fareed, et al., "Pharmacologic Validation of the Antithrombotic and Vascular Effects of Defibrotide," Adv. in Vascular Path., 171-177 (1990).

Other Reference Publication (26):
Fareed, et al., "Pharmacologic Profiling of Defibrotide in Experimental Models," Seminars in Thromb. and Hemostasis, 14:27-37 (1988).

Other Reference Publication (31):
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Other Reference Publication (36):
Lobel et al., "Selective Stimulation of Coronary Vascular PGI.sub.2 But Not of Platelet Thromboxane Formation by Defibrotide in the Platelet Perfused Heart," Naunyn-Schmiedeberg's Archives of Pharmacol., 331:125-130 (1985).

Other Reference Publication (38):
Marni et al., "Protection of Kidney from Postischemic Reperfusion Injury in Rats Treated with Defibrotide," Transplantation Proceedings, 22:2226-2229 (1990).

Other Reference Publication (43):
Niada et al., "PGI.sub.2 -Generation and Antithrombotic Activity of Orally Administered Defibrotide," Pharmacological Res. COmm., 14:949-957 (1982).

Other Reference Publication (45):
Niada et al., "Cardioprotective Effects of Defibrotide in Acute Lethal and Nonlethal Myocardial Ischemia in the Cat," Haemostasis, 16:18-25 (1986).

Other Reference Publication (49):
Pescador et al, "Pharmacokinetics of Defibrotide and of its Profibrinolytic Activity in the Rabbit," Thromb. Res., 30:1-11 (1983).

Other Reference Publication (51):
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by Peripheral Arterial Occlusive Disease," Intl J. Clin. Pharm., Ther. & Toxic., 26:249-252 (1988).

Other Reference Publication (58):
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CLAIMS:

1. A method of treating a disease condition in a patient selected from the group consisting of vascular disease, veno-occlusive disease, thrombotic microangiopathy, acquired thrombopathy, glomular proteinuria, renal failure, nephrogenic hypertension, hemolytic uremic syndrome, primary anti-phospholipid antibody syndrome, prothrombotic state secondary to anti-phospholipid antibody, anti-phospholipid antibody dependent acute myocardial infarction, acquired platelet abnormality, adult respiratory distress syndrome, subendocardial myocardial infarction, soft tissue necrosis, arthralgia, tuberculosis, and herpes, comprising the following steps:

(a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being observable characteristics of a patient which deviate from a normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,

(b) administering to the patient a dose of a therapeutic compound wherein the amount is between 40 mg/kg patient body weight per day to 250 mg/kg patient body weight per day comprising defibrotide,

(c) screening a panel of second messengers and signal transducers and selecting a repair marker, the intensity of which increases following administration of defibrotide, where intensity is the extent to which the state of the repair marker differs from its state in the normal condition, said repair marker being the concentration of a compound which participates in a cellular regulatory pathway which operates through protein kinase A, protein kinase C, or G-protein,

(d) administering defibrotide at a dose level incrementally higher than the previous dose,

(e) repeating step (d) each time the intensity of the repair marker increases,

(f) repeating steps (d) and (e) until the intensity of the repair marker in step (c) no longer increases,

(g) continuing administration of defibrotide at the highest dose level attained in step (f) until the intensity of the repair marker returns to the normal condition, and

(h) administering defibrotide at a dose level incrementally higher than the previous dose and repeating steps (c), (d), (e),(f) and (g) with one or more additional repair markers until all disease markers of said set of disease markers no longer deviate from the normal condition.

4. The method of claim 1 wherein defibrotide is administered intravenously, orally or topically.

5. The method of claim 1 wherein the dose of defibrotide is from about 40 mg/kg patient body weight per day to about 350 mg/kg patient body weight per day and defibrotide is high molecular weight defibrotide.

6. The method of claim 1 wherein the dose of defibrotide is from about 40 mg/kg patient body weight per day to about 600 mg/kg patient body weight per day and defibrotide is low molecular weight defibrotide.

7. A method of treating a disease condition in a patient selected from the group consisting of vascular disease, veno-occlusive disease, thrombotic microangiopathy,

acquired thrombopathy, glomular proteinuria, renal failure, nephrogenic hypertension, hemolytic uremic syndrome, primary anti-phospholipid antibody syndrome, prothrombotic state secondary to anti-phospholipid antibody, anti-phospholipid antibody dependent acute myocardial infarction, acquired platelet abnormality, adult respiratory distress syndrome, subendocardial myocardial infarction, soft tissue necrosis, arthralgia, tuberculosis, and herpes, comprising the following steps:

(a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being observable characteristics of a patient which deviate from a normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,

(b) administering to the patient a dose of a therapeutic compound wherein the amount is between 40 mg/kg patient body weight per day to 250 mg/kg patient body weight per day comprising defibrotide,

(c) screening a panel of second messengers and signal transducers and selecting a repair marker, the intensity of which increases following administration of defibrotide, where intensity is the extent to which the state of the repair marker differs from its state in the normal condition, the repair marker being the concentration of a compound which participates in a cellular regulatory pathway which operates through protein kinase A, protein kinase C, or G-protein,

(d) administering defibrotide at a dose level incrementally higher than the previous dose,

(e) repeating step (d) each time the intensity of the repair marker increases,

(f) repeating steps (d) and (e) until the intensity of the repair marker in step (c) no longer increases,

(g) administering defibrotide at the dose level where the intensity of the repair marker no longer increases until the intensity of the repair marker returns to the normal condition,

(h) administering defibrotide at a dose level incrementally higher than the previous dose and repeating steps (c), (d), (e), (f) and (g) with one or more additional repair markers until all disease markers of said set of disease markers no longer deviate from the normal condition, and

(i) administering defibrotide at a dose level incrementally higher than the previous dose given in step (h) and repeating steps (c), (d), (e), (f) and (g) until the intensity of a universal marker, vWAg, returns to the concentration found in an uninfected individual.

9. A method of treating a disease condition in a patient selected from the group consisting of vascular disease, veno-occlusive disease, thrombotic microangiopathy, acquired thrombopathy, glomular proteinuria, renal failure, nephrogenic hypertension, hemolytic uremic syndrome, primary anti-phospholipid antibody syndrome, prothrombotic state secondary to anti-phospholipid antibody, anti-phospholipid antibody dependent acute myocardial infarction, acquired platelet abnormality, adult respiratory distress syndrome, subendocardial myocardial infarction, soft tissue necrosis, arthralgia, tuberculosis, and herpes, comprising the following steps:

(a) determining the initial state of a set of disease markers associated with the disease condition, the disease markers being observable characteristics of a patient which deviate from a normal condition due to the disease state and wherein each disease marker in the set has a predetermined reference range which is indicative of the normal condition,

(b) administering to the patient a dose of a therapeutic compound comprising defibrotide, wherein the dose of defibrotide is at a level which raises a universal marker to at least five times its normal level, the universal marker being, von Willebrandt antigen (vWAg), a constitutively expressed molecule which is

transcriptionally activated by the therapeutic compound in all disease states, and

(c) continuing to administer defibrotide at the dose level of step (b) until the universal marker returns to its normal level.

11. The method of claims 1, 5 or 6 wherein the administration of defibrotide induces fibrinolysis.

12. The method of claim 11 wherein the dose of defibrotide in step (b) is from about 240 mg/kg patient body weight per day to about 300 mg/kg patient body weight per day.

13. The method of claims 1, 5 or 6 wherein the administration of defibrotide induces activation of protein kinase A or protein kinase C.

14. The method of claim 13 wherein the dose of defibrotide in step (b) is from about 240 mg/kg patient body weight per day to about 300 mg/kg patient body weight per day.

15. The method of claims 1, 5 or 6 wherein the administration of defibrotide induces antithrombotic action.

16. The method of claim 15 wherein the dose of defibrotide in step (b) is from about 80 mg/kg patient body weight per day to about 200 mg/kg patient body weight per day.

17. The method of claims 1, 5 or 6 wherein the administration of defibrotide induces proplatelet action.

18. The method of claim 17 wherein the dose of defibrotide in step (b) is from about 120 mg/kg patient body weight per day to about 200 mg/kg patient body weight per day.

19. The method of claims 1, 5 or 6 wherein the disease condition is a prothrombotic state secondary to anti-phospholipid antibody or primary anti-phospholpid antibody disease and wherein the dose of defibrotide in step (b) is from about 60 mg/kg patient body weight per day to about 200 mg/kg patient body weight per day.

20. The method of claims 1, 5 or 6 wherein the disease condition is renal failure, nephrogenic hypertension, thrombotic microangiopathy, or hemolytic uremic syndrome and wherein the dose of defibrotide in step (b) is at least 60 mg/kg patient body weight per day.

21. The method of claim 20 wherein the dose of defibrotide in step (b) is from about 150 mg/kg patient body weight per day to about 250 mg/kg patient body weight per day.

22. The method of claims 1, 5, 6 wherein the disease condition is anti-phospholipid antibody dependent acute myocardial infarction or adult respiratory distress syndrome and wherein the dose of defibrotide in step (b) is from about 60 mg/kg patient body weight per day to about 200 mg/kg patient body weight per day.

23. The method of claims 1, 5 or 6 wherein the disease condition is acquired thrombopathy and wherein the dose of defibrotide in step (b) is from about 120 mg/kg patient body weight per day to about 250 mg/kg patient body weight per day.

24. The method of claim 1, 5 or 6 wherein the administration of defibrotide induces activation or repression of genomic transcription.

25. The method of claim 24 wherein the dose of defibrotide in step (b) is from about 40 mg/kg patient body weight per day to about 400 mg/kg patient body weight per day.

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☐ 1. Document ID: US 6254558 B1

L3: Entry 1 of 44 File: USPT Jul 3, 2001

US-PAT-NO: 6254558
DOCUMENT-IDENTIFIER: US 6254558 B1

TITLE: Method for producing a therapeutic system in the form of plaster

DATE-ISSUED: July 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Meconi; Reinhold	Neuwied			DEX
Rademacher; Tina	Bad Breisig			DEX
Schumann; Klaus	Neuwied			DEX
Seibertz; Frank	Bad Honningen			DEX

US-CL-CURRENT: 602/6; 424/443

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 6245782 B1

L3: Entry 2 of 44 File: USPT Jun 12, 2001

US-PAT-NO: 6245782
DOCUMENT-IDENTIFIER: US 6245782 B1

TITLE: Methods of inhibiting platelet activation with selective serotonin reuptake inhibitors

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Serebruany; Victor L.	Ellicott City	MD		
Gurbel; Paul A.	Baltimore	MD		
O'Connor; Christopher M.	Durham	NC		

US-CL-CURRENT: 514/321; 514/469, 514/640, 514/654, 514/753

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 6221383 B1

L3: Entry 3 of 44 File: USPT Apr 24, 2001

US-PAT-NO: 6221383
DOCUMENT-IDENTIFIER: US 6221383 B1

TITLE: Solubility parameter based drug delivery system and method for altering drug saturation concentration

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miranda; Jesus	Miami	FL		
Sablotsky; Steven	Miami	FL		

US-CL-CURRENT: 424/449; 424/448

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 4. Document ID: US 6046172 A

L3: Entry 4 of 44 File: USPT Apr 4, 2000

US-PAT-NO: 6046172
DOCUMENT-IDENTIFIER: US 6046172 A

TITLE: Hydrolytically processed oligodeoxyribonucleotides and their pharmaceutical compositions

DATE-ISSUED: April 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ennio; Lanzarotti	Milan			ITX
Marisa; Mantovani	Como			ITX
Giuseppe; Prino	Milan			ITX
Roberto; Porta	Como			ITX
Armando; Cedro	Milan			ITX
Danilo; Moltrasio	Como			ITX

US-CL-CURRENT: 514/44; 536/23.1, 536/25.4, 536/25.41

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 5. Document ID: US 6024976 A

L3: Entry 5 of 44 File: USPT Feb 15, 2000

US-PAT-NO: 6024976

DOCUMENT-IDENTIFIER: US 6024976 A

TITLE: Solubility parameter based drug delivery system and method for altering drug saturation concentration

DATE-ISSUED: February 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miranda; Jesus	Miami	FL		
Sablotsky; Steven	Miami	FL		

US-CL-CURRENT: 424/449; 424/448

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 6. Document ID: US 5977083 A

L3: Entry 6 of 44 File: USPT Nov 2, 1999

US-PAT-NO: 5977083
DOCUMENT-IDENTIFIER: US 5977083 A

TITLE: Method for using polynucleotides, oligonucleotides and derivatives thereof to treat various disease states

DATE-ISSUED: November 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Burcoglu; Arsinur	Pittsburgh	PA	15238	

US-CL-CURRENT: 514/44; 435/5, 435/6, 536/23.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 7. Document ID: US 5719197 A

L3: Entry 7 of 44 File: USPT Feb 17, 1998

US-PAT-NO: 5719197
DOCUMENT-IDENTIFIER: US 5719197 A

TITLE: Compositions and methods for topical administration of pharmaceutically active agents

DATE-ISSUED: February 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kanios; David P.	Miami	FL		
Gentile; Joseph A.	Plantation	FL		
Mantelle; Juan A.	Miami	FL		
Sablotsky; Steven	Miami	FL		

US-CL-CURRENT: 514/772.6; 424/435, 424/443, 514/781, 514/782

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw. Desc | Image

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☐ 8. Document ID: US 5698206 A

L3: Entry 8 of 44 File: USPT Dec 16, 1997

US-PAT-NO: 5698206
DOCUMENT-IDENTIFIER: US 5698206 A

TITLE: Topical composition for the treatment of spider veins

DATE-ISSUED: December 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Becker; Philip E.	Jupiter	FL		
Doepker; Mary Lou	Miami	FL		

US-CL-CURRENT: 424/401; 424/195.17, 424/63, 424/64, 424/66, 424/757, 424/764

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWMC | Draw. Desc | Image

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☐ 9. Document ID: US 5656286 A

L3: Entry 9 of 44 File: USPT Aug 12, 1997

US-PAT-NO: 5656286
DOCUMENT-IDENTIFIER: US 5656286 A

TITLE: Solubility parameter based drug delivery system and method for altering drug saturation concentration

DATE-ISSUED: August 12, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Miranda; Jesus	Miami	FL		
Sablotsky; Steven	Miami	FL		

US-CL-CURRENT: 424/449; 424/448

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 10. Document ID: US 5646268 A

L3: Entry 10 of 44 File: USPT Jul 8, 1997

US-PAT-NO: 5646268
DOCUMENT-IDENTIFIER: US 5646268 A

TITLE: Process producing lower molecular weight range oligodeoxyribonucleotides

DATE-ISSUED: July 8, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lanzarotti; Ennio	Milan			ITX
Mantovani; Marisa	Villa Guardia			ITX
Prino; Giuseppe	Milan			ITX
Porta; Roberto	Cernobbio			ITX
Cedro; Armando	Cislago			ITX
Moltrasio; Danilo	Rovellasca			ITX

US-CL-CURRENT: 536/25.4; 536/23.1, 536/25.41

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 11. Document ID: US 5646127 A

L3: Entry 11 of 44 File: USPT Jul 8, 1997

US-PAT-NO: 5646127
DOCUMENT-IDENTIFIER: US 5646127 A

TITLE: Treatment of cardiac ischemia by administration of a fraction of partially depolymerized DNA

DATE-ISSUED: July 8, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lanzarotti; Ennio	Milan			ITX
Mantovani; Marisa	Villa Guardia			ITX
Prino; Giuseppe	Milan			ITX
Porta; Roberto	Cernobbio			ITX
Armando; Cedro	Cislago			ITX
Moltrasio; Danilo	Rovellasca			ITX

US-CL-CURRENT: 514/44; 536/23.1, 536/25.4, 536/25.41

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 12. Document ID: US 5624912 A

L3: Entry 12 of 44 File: USPT Apr 29, 1997

US-PAT-NO: 5624912
DOCUMENT-IDENTIFIER: US 5624912 A

TITLE: Method of treating HIV infection and related secondary infections with defibrotide

DATE-ISSUED: April 29, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Burcoglu; Arsinur	Pittsburg	PA	15238	
Wagner; Marc	Pittsburg	PA	15221	

US-CL-CURRENT: 514/44; 514/924, 514/934

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 13. Document ID: US 5446070 A

L3: Entry 13 of 44 File: USPT Aug 29, 1995

US-PAT-NO: 5446070
DOCUMENT-IDENTIFIER: US 5446070 A

TITLE: Compositions and methods for topical administration of pharmaceutically active agents

DATE-ISSUED: August 29, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mantelle; Juan A.	Miami	FL		

US-CL-CURRENT: 514/772.6; 424/485, 424/486, 424/487, 424/488, 514/781, 514/782

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 14. Document ID: US 5345932 A

L3: Entry 14 of 44 File: USPT Sep 13, 1994

US-PAT-NO: 5345932
DOCUMENT-IDENTIFIER: US 5345932 A

TITLE: Method and system for monitoring of blood constituents in vivo

DATE-ISSUED: September 13, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yafuso; Masao	El Toro	CA		
Harker; Laurence A.	Atlanta	GA		

US-CL-CURRENT: 600/368; 600/506

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 15. Document ID: US 5223609 A

L3: Entry 15 of 44 File: USPT Jun 29, 1993

US-PAT-NO: 5223609
DOCUMENT-IDENTIFIER: US 5223609 A

TITLE: Process for obtaining chemically defined and reproducible polydeoxyribonucleotides

DATE-ISSUED: June 29, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fedeli; Gianfranco	Milan			ITX
Diamantini; Giuseppe	Appiano Gentile			ITX
Mantovani; Marisa	Villa Guardia			ITX
Prino; Giuseppe	Milan			ITX

US-CL-CURRENT: 536/23.1; 435/91.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 16. Document ID: US 5195963 A

L3: Entry 16 of 44 File: USPT Mar 23, 1993

US-PAT-NO: 5195963
DOCUMENT-IDENTIFIER: US 5195963 A

TITLE: Method and system for monitoring of blood constituents in vivo

DATE-ISSUED: March 23, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yafuso; Masao	El Toro	CA		
Harker; Laurence A.	Atlanta	GA		

US-CL-CURRENT: 604/504; 128/898, 600/322, 600/368

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 17. Document ID: US 5116617 A

L3: Entry 17 of 44 File: USPT May 26, 1992

US-PAT-NO: 5116617
DOCUMENT-IDENTIFIER: US 5116617 A

TITLE: Pharmaceutical composition for topical use in the treatment of the capillary fragility

DATE-ISSUED: May 26, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mantovani; Marisa	Villa Guardia			ITX
Porta; Roberto	Cernobbio			ITX
Prino; Giuseppe	Milan			ITX

US-CL-CURRENT: 424/401; 514/44, 514/822, 514/969

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 18. Document ID: US 5081109 A

L3: Entry 18 of 44 File: USPT Jan 14, 1992

US-PAT-NO: 5081109
DOCUMENT-IDENTIFIER: US 5081109 A

TITLE: Pharmaceutical composition and method for the therapy of peripheral arteriopathies

DATE-ISSUED: January 14, 1992

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ulutin; Orhan N.	Istanbul			TRX

US-CL-CURRENT: 514/44; 514/824, 536/23.1, 536/25.41

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 19. Document ID: US 4985552 A

L3: Entry 19 of 44 File: USPT Jan 15, 1991

US-PAT-NO: 4985552
DOCUMENT-IDENTIFIER: US 4985552 A

TITLE: Process for obtaining chemically defined and reproducible polydeoxyribonucleotides

DATE-ISSUED: January 15, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fedeli; Gianfranco	Milan			ITX
Diamantini; Giuseppe	Appiano; Gentile			ITX
Maontovani; Marisa	Villas Guardia			ITX
Prino; Giuseppe	Milan			ITX

US-CL-CURRENT: 536/25.4; 536/25.42, 536/25.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 20. Document ID: US 4938873 A

L3: Entry 20 of 44 File: USPT Jul 3, 1990

US-PAT-NO: 4938873
DOCUMENT-IDENTIFIER: US 4938873 A

TITLE: Method for preventing blood coaguli from being formed in the extra-body circuit of dialysis apparatus and composition useful therefor

DATE-ISSUED: July 3, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rossi; Renato	Casnate-con-Bernate			ITX

US-CL-CURRENT: 210/646; 210/647

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 21. Document ID: US 4693995 A

L3: Entry 21 of 44 File: USPT Sep 15, 1987

US-PAT-NO: 4693995
DOCUMENT-IDENTIFIER: US 4693995 A

TITLE: Pharmaceutical composition for the treatment of acute myocardial ischemia

DATE-ISSUED: September 15, 1987

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Prino; Giuseppe	Milan			ITX
Mantovani; Marisa	Villa Guardia Como			ITX
Niada; Riccardo	Varese			ITX

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 22. Document ID: US 4649134 A

L3: Entry 22 of 44 File: USPT Mar 10, 1987

US-PAT-NO: 4649134
DOCUMENT-IDENTIFIER: US 4649134 A

TITLE: Pharmaceutical composition containing defibrotide for the treatment of states of acute renal insufficiency

DATE-ISSUED: March 10, 1987

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bonomini; Vittorio	Bologna			ITX

US-CL-CURRENT: 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

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☐ 23. Document ID: JP 03099019 A

L3: Entry 23 of 44 File: JPAB Apr 24, 1991

PUB-NO: JP403099019A
DOCUMENT-IDENTIFIER: JP 03099019 A
TITLE: PHARMACEUTICAL COMPOSITION FOR TOPICAL USE IN TREATMENT OF CAPILLARY FRAGILITY

PUBN-DATE: April 24, 1991

INVENTOR-INFORMATION:

NAME	COUNTRY
MANTOVANI, MARISA	
PORTA, ROBERTO	
PRINO, GIUSEPPE	

INT-CL (IPC): A61K 35/42; A61K 31/70

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

☐ 24. Document ID: JP 02092363 A

L3: Entry 24 of 44 File: JPAB Apr 3, 1990

PUB-NO: JP402092363A
DOCUMENT-IDENTIFIER: JP 02092363 A
TITLE: DIALYSIS APPARATUS

PUBN-DATE: April 3, 1990

INVENTOR-INFORMATION:

NAME	COUNTRY
ROSSI, RENATO	

INT-CL (IPC): A61M 1/14; A61M 1/36

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 25. Document ID: WO 9848843 A1

L3: Entry 25 of 44 File: EPAB Nov 5, 1998

PUB-NO: WO009848843A1
DOCUMENT-IDENTIFIER: WO 9848843 A1
TITLE: METHOD OF TREATING HIV INFECTION AND RELATED SECONDARY INFECTIONS THEREOF

PUBN-DATE: November 5, 1998

INVENTOR-INFORMATION:

NAME	COUNTRY
BURCOGLU, ARSINUR	US

INT-CL (IPC): A61 K 48/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 26. Document ID: US 5624912 A

L3: Entry 26 of 44 File: EPAB Apr 29, 1997

PUB-NO: US005624912A
DOCUMENT-IDENTIFIER: US 5624912 A
TITLE: Method of treating HIV infection and related secondary infections with defibrotide

PUBN-DATE: April 29, 1997

INVENTOR-INFORMATION:

NAME	COUNTRY
BURCOGLU, ARSINUR	US
WAGNER, MARC	US

INT-CL (IPC): A61 K 48/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 27. Document ID: WO 9415621 A1

L3: Entry 27 of 44 File: EPAB Jul 21, 1994

PUB-NO: WO009415621A1
DOCUMENT-IDENTIFIER: WO 9415621 A1
TITLE: METHOD FOR USING POLYNUCLEOTIDES, OLIGONUCLEOTIDES AND DERIVATIVES THEREOF TO TREAT VARIOUS DISEASE STATES

PUBN-DATE: July 21, 1994

INVENTOR-INFORMATION:

NAME	COUNTRY
BURCOGLU, ARSINUR	US

INT-CL (IPC): A61K 31/70; C12N 15/11; C07H 21/00
EUR-CL (EPC): A61K031/70; C12N015/11

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 28. Document ID: US 5081109 A

L3: Entry 28 of 44 File: EPAB Jan 14, 1992

PUB-NO: US005081109A
DOCUMENT-IDENTIFIER: US 5081109 A
TITLE: PHARMACEUTICAL COMPOSITION AND METHOD FOR THE THERAPY OF PERIPHERAL ARTERIOPATHIES

PUBN-DATE: January 14, 1992

INVENTOR-INFORMATION:

NAME	COUNTRY
ULUTIN, ORHAN N	TR

INT-CL (IPC): A61K 27/00
EUR-CL (EPC): A61K031/70; A61K035/12, C07H021/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
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☐ 29. Document ID: EP 416678 A1

L3: Entry 29 of 44 File: EPAB Mar 13, 1991

PUB-NO: EP000416678A1
DOCUMENT-IDENTIFIER: EP 416678 A1
TITLE: Topical compositions containing Defibrotide.

PUBN-DATE: March 13, 1991

INVENTOR-INFORMATION:

NAME	COUNTRY
MANTOVANI, MARISA	IT
PRINO, GIUSEPPE	IT
PORTA, ROBERTO	IT

INT-CL (IPC): A61K 9/06; A61K 31/70
EUR-CL (EPC): A61K031/70

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 30. Document ID: US 4985552 A

L3: Entry 30 of 44 File: EPAB Jan 15, 1991

PUB-NO: US004985552A
DOCUMENT-IDENTIFIER: US 4985552 A
TITLE: Process for obtaining chemically defined and reproducible polydeoxyribonucleotides

PUBN-DATE: January 15, 1991

INVENTOR-INFORMATION:

NAME	COUNTRY
FEDELI, GIANFRANCO	IT
DIAMANTINI, GIUSEPPE	IT
MAONTOVANI, MARISA	IT
PRINO, GIUSEPPE	IT

INT-CL (IPC): C07N 1/00
EUR-CL (EPC): C07H001/08

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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defibrotide	44

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L4: Entry 2 of 2 File: USPT Aug 29, 1995

DOCUMENT-IDENTIFIER: US 5446070 A
TITLE: Compositions and methods for topical administration of pharmaceutically active agents

Brief Summary Paragraph Right (9):
U.S. Pat. No. 4,937,078 to Mezei, et al. describes a liposome encapsulated local anesthetic or analgesic agent that is said to provide, when applied to the skin or mucous membrane, greater local anesthesia and analgesia than the same agents incorporated in conventional vehicles such as ointments, creams, or lotions. These liposomal films are preferably applied under occlusion.

Detailed Description Paragraph Type 0 (68):
ANTITHROMBOTIC such as Anagrelide, Argatroban, Cilostazol, Daltroban, Defibrotide, Enoxaparin, Fraxiparine.RTM., Indobufen, Lamoparan, Ozagrel, Picotamide, Plafibride, Tedelparin, Ticlopidine, Triflusal

WEST Search History

DATE: Tuesday, April 02, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L8	defibrotide same transfection	0	L8
L7	L3 and transfection	2	L7
L6	L3 and cationic	0	L6
L5	L1 and oligonucleotide$	3	L5
L4	L3 and liposome$	2	L4
L3	defibrotide	44	L3
L2	L1 and liposome$	3	L2
L1	deoxyribonucleotide$ same (wound adj1 healing)	4	L1

END OF SEARCH HISTORY